Enantioselective Synthesis of Atropisomeric Benzamides through Peptide-Catalyzed Bromination

Supporting Information (Part I)

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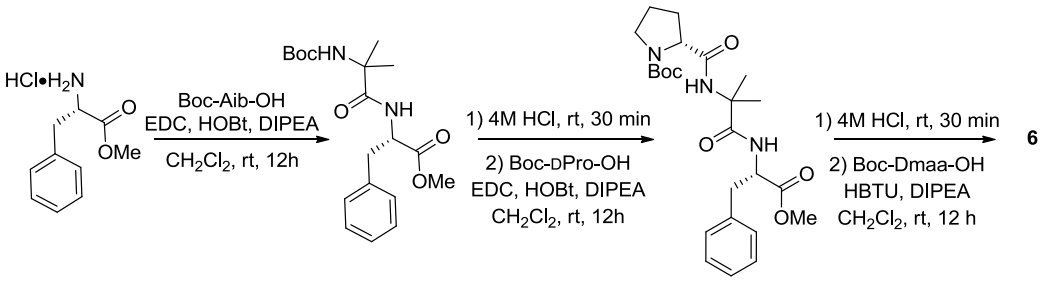
I. General Procedures.

Unless otherwise noted, all reagents were obtained from commercial suppliers and used without purification. Tetrahydrofuran (THF), diethyl ether, dichloromethane (CH_2Cl_2), and toluene were obtained from a Seca Solvent System by GlassContour (solvent dried over alumina under an Ar atmosphere). Chloroform (ACS grade) was purchased from J.T. Baker. Commercially available dibromodimethylhydantoin (DBDMH) was purified by recrystallization from hot water. ^{1}H NMR spectra were obtained on Bruker 400 MHz or 500 MHz spectrometers. Unless otherwise noted, all NMR spectra were acquired at ambient temperature. Spectral data are reported as follows: chemical shift (multiplicity [singlet (s), broad singlet (bs), doublet (d), triplet (t), quartet (q), heptet (hept), multiplet (m), doublet of doublets (dd), doublet of doublet of doublets (ddd), doublet of triplets (dt), and doublet of quartet (dq)], coupling constants (Hz), integration). Chemical shifts are reported in ppm and coupling constants are reported in Hz. ^{1}H resonances are referenced to $CHCl_3$ (7.26 ppm), MeOH (3.31 ppm), or DMSO (2.50 ppm). ^{13}C spectra were obtained on Bruker 100 MHz or 125 MHz spectrometers. ^{13}C resonances are referenced to $CDCl_3$ (77.16 ppm) or MeOD (49.00 ppm). Infrared spectra were obtained on a Nicolet 6700 ATR/FT-IR spectrometer and ν_{max} are partially reported (cm^{-1}). For characterization, high-resolution liquid chromatography-mass spectrometry (HR-LC/MS) was performed on a Waters XEVO instrument equipped with ESI, a QToF mass spectrometer, and a photodiode array detector. For crude analysis, ultra high-performance liquid chromatography-mass spectrometry (UPLC/MS) was performed on a Waters UPLC/MS instrument equipped with a reverse-phase C18 column (1.7 μm particle size, 2.1 × 50 mm), dual atmospheric pressure chemical ionization (API)/electrospray (ESI) mass spectrometry detector, and photodiode array detector. Analytical thin-layer chromatography (TLC) was performed using Silica Gel 60 Å F254 pre-coated plates (0.25 mm thickness). TLC R_f values are reported, with visualization accomplished by irradiation with a UV lamp or with appropriate stain. Flash column chromatography was performed using Silica Gel 60 Å (32-62 micron) or using a Biotage SP4 purification system. Optical rotations were recorded on a Perkin-Elmer Polarimeter 341 at the sodium D line (1.0 dm path length). Reverse-phase HPLC analysis and purification were conducted with an Agilent 1100 series instrument equipped with a diode array detector (λ = 230 nm) and columns (chiral supports) from Daicel Chemical Industries (Chiralpak AD-H, Chiralcel OD-H, and Chiralpak IC) at column temperature of 30 ^{o}C.

II. Solution Phase Synthesis of Peptide Catalyst 6.



Peptide Coupling 1. Catalyst **6** was synthesized by solution phase peptide synthesis using the Boc protection strategy. A flask was charged with phenylalanine methyl ester hydrochloride (863 mg, 4.00 mmol), *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide (EDC) (997 mg, 5.20 mmol), 1-hydroxybenzotriazole (HOBt) (919 mg, 6.00 mmol), and *N*-Boc-α-aminoisobutyric acid (Boc-Aib-OH) (1.06 g, 5.20 mmol). Dichloromethane (20 mL) and diisopropylethylamine (DIPEA) (0.91 mL, 5.20 mmol) were added, and the reaction mixture was stirred at ambient temperature for 12 h. The reaction mixture was transferred to a separatory funnel, diluted with 30 mL dichloromethane, and washed with saturated 0.5 M citric acid (1 × 50 mL) and saturated aqueous sodium bicarbonate (1 × 50 mL). The organic layer was then dried with sodium sulfate, filtered, and concentrated to give crude dipeptide Boc-Aib-Phe-OMe.

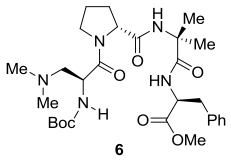
Deprotection 1. To the flask containing crude dipeptide Boc-Aib-Phe-OMe was added 5 mL of 4M HCl in dioxane at ambient temperature. The reaction was stirred for 30 min under nitrogen and then the reaction was concentrated under a vigorous stream of dry nitrogen for 1 h. At this time, volatiles were fully removed by concentrating under reduced pressure with a rotary evaporator and then placing the flask under high vacuum for at least 1 hour.

Peptide Coupling 2. The second peptide coupling was carried out in the same manner as Peptide Coupling 1 using EDC (997 mg, 5.20 mmol), HOBt (919 mg, 6.00 mmol), *N*-Boc-D-proline (Boc-DPro-OH) (1.12 g, 5.20 mmol), dichloromethane (20 mL), and DIPEA (0.91 mL, 5.20 mmol). The workup was carried out as described previously.

Deprotection 2. Deprotection of the crude tripeptide Boc-DPro-Aib-Phe-OMe was carried out in the same manner as Deprotection 1 above.

Peptide Coupling 3. After Boc deprotection, Boc-β-Dmaa-OH (synthesized according to literature procedures)[1] (928 mg, 5.20 mmol) was added to the reaction flask and suspended in dichloromethane (20mL). 2-(1H-Benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluoro-phosphate (HBTU) (1.90 g, 5.00 mmol) and DIPEA (0.87 mL, 5.00 mmol) were added, and the reaction mixture was stirred at ambient temperature for 12 h. The reaction mixture was then diluted with 100 mL dichloromethane, transferred to a separatory funnel, and washed with 100 mL of a saturated sodium bicarbonate. The organic phase was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was purified by reverse phase column chromatography using a Biotage SP4 system with a KP-C18-HS column (10% methanol/water to 90% methanol/water; flow rate = 45 mL/min). The fractions were pooled and

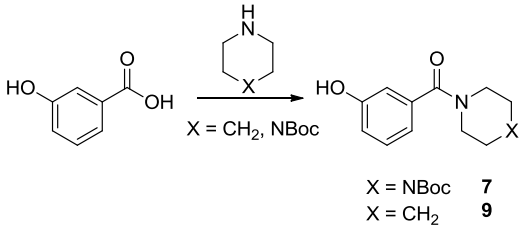
concentrated under rotary evaporation to yield purified peptide **6** as a white foam (518 mg, 23% yield).

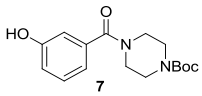


6

$[\alpha]_D^{20.0}$ +31.6 (*c* 0.50, $CHCl_3$); **TLC** R_f 0.42 (9:1 CH_2Cl_2:MeOH, ninhydrin stain); **IR** (FT-ATR, cm^{-1}) 2947, 1636, 1513, 1444, 1167, 1020; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.29-7.22 (m, 2H), 7.21-7.16 (m, 3H), 7.12 (d, *J* = 7.9 Hz, 1H), 6.90 (s, 1H), 5.76 (bs, 1H), 4.80 (dd, *J* = 14.5, 7.1 Hz, 1H), 4.42-4.33 (m, 2H), 3.88-3.82 (m, 1H), 3.63 (s, 3H), 3.59-3.52 (m, 1H), 3.10 (ddd, *J* = 32.0, 13.8, 6.8 Hz, 2H), 2.73-2.43 (m, 2H), 2.30 (s, 6H), 2.27-2.18 (m, 1H), 2.12-2.01 (m, 1H), 2.02-1.84 (m, 2H), 1.47 (s, 3H), 1.42 (s, 9H), 1.36 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 174.1, 172.6, 171.1, 170.8, 155.9, 136.8, 129.5, 128.4, 126.8, 80.0, 61.2, 59.8, 47.2, 53.5, 52.1, 50.8, 47.5, 45.7, 38.2, 28.5, 28.4, 26.1, 24.9, 24.8; **LCMS** (ESI) *m/z* calc'd for $C_{29}H_{46}N_5O_7$ $[M+H]^+$ 576.3397, found 576.3397.

III. Substrate Syntheses and Characterization.





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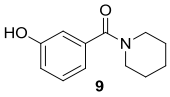
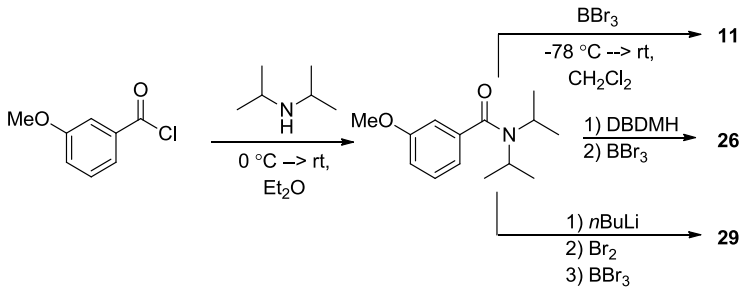
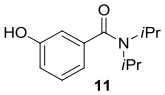
***tert*-butyl-4-(3-hydroxybenzoyl)piperazine-1-carboxylate (7).** A flask was charged with 3-hydroxybenzoic acid (618 mg, 4.50 mmol) and *tert*-butyl-piperazine-1-carboxylate[2] (1.00 g, 5.40 mmol). Dichloromethane (22.5 mL) and diisopropylethylamine (0.98 mL, 5.60 mmol) were then added, followed by HBTU (2.12 g, 5.60 mmol). The reaction was allowed to stir for 12 h at room temperature under a nitrogen atmosphere. At this time, the reaction was diluted with CH_2Cl_2 and washed with 0.5 M citric acid. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated. Recrystallization from hot ethyl acetate and hexanes afforded 813 mg (59% yield) of a white crystalline solid. **TLC** R_f 0.32 (1:1 Hexanes:EtOAc); **IR** (FT-ATR, cm^{-1}) 3263, 2977, 1696, 1422, 1241, 1167; **^{1}H NMR** (500 MHz, MeOD) δ 7.27 (t, *J* = 7.8 Hz, 1H), 6.89 (dd, *J* = 8.2, 2.4 Hz, 1H), 6.86 (d, *J* = 7.5, 1H), 6.81 (s, 1H), 3.71 (bs, 2H), 3.52 (bs, 2H), 3.43 (bs, 4H), 1.47 (s, 9H); **^{13}C NMR** (125 MHz, MeOD) δ 172.7, 159.0, 156.2, 137.8, 131.0, 118.8, 118.1, 114.7, 81.7, 43.2, 28.6; **LCMS** (ESI) *m/z* calc'd for $C_{16}H_{22}NNaO_4$ $[M+Na]^+$ 329.1478, found 329.1504.



(3-hydroxyphenyl)(piperidin-1-yl)methanone (9). A flask was charged with 3-hydroxybenzoic acid (2.00 g, 14.5 mmol) and placed under positive nitrogen pressure. Dichloromethane (40 mL) and diisopropylethylamine (2.40 mL, 14.5 mmol) were then added, followed by piperidine addition (1.43 mL, 14.5 mmol). The reaction vessel was then cooled to 0 °C. In a separate flask, EDC·HCl (3.62 g, 18.9 mmol) and HOBt·H_2O (2.66 g, 17.4 mmol) were dissolved in dichloromethane and this solution was added dropwise to the reaction at 0 °C. The reaction was allowed to stir for 12 h at room temperature. At this time, the reaction was quenched with 0.5 M citric acid and the organic layer was separated. The aqueous layer was extracted three times with CH_2Cl_2 and the organic layers were combined, dried over Na_2SO_4, filtered, and concentrated. Recrystallization from hot ethanol afforded 2.26 g (76% yield) of a white crystalline solid. **TLC** R_f 0.29 (1:1 Hexanes:EtOAc); **IR** (FT-ATR, cm^{-1}) 3144, 2950, 1567, 1451, 1222, 742; **^{1}H NMR** (500 MHz, MeOD) δ 7.25 (t, *J* = 7.9 Hz, 1H), 6.86 (ddd, *J* = 8.2, 2.5, 0.9 Hz, 1H), 6.83-6.79 (m, 1H), 6.77 (dd, *J* = 2.2, 1.8 Hz, 1H), 3.65 (bs, 2H), 3.41(bs, 2H), 1.77-1.69 (m, 2H), 1.65 (bs, 2H), 1.53 (bs, 2H); **^{13}C NMR** (125 MHz, MeOD) δ 172.4, 158.9, 138.6, 130.9, 118.4, 117.7, 114.4, 50.0, 44.2, 27.6, 26.8, 25.5; **LCMS** (ESI) *m/z* calc'd for $C_{12}H_{16}NO_2$ $[M+H]^+$ 206.1181, found 206.1168.

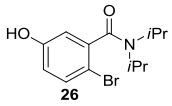




3-hydroxy-*N*,*N*-diisopropylbenzamide (11). Step 1:[3] To a flame-dried flask under positive nitrogen pressure, 3-methoxybenzoyl chloride (2.00 mL, 14.6 mmol) and diethyl ether (61 mL) were added and the flask was cooled to 0 °C. Diisopropylamine (5.10 mL, 36.5 mmol) was added dropwise and the reaction was allowed to stir for 4 h at room temperature. The reaction was quenched with 0.1 M HCl and the organic layer was separated. The organic layer was washed with 0.1 M HCl, brine, and 0.1 M NaOH, then dried over $MgSO_4$. The pale yellow solid obtained (3.01 g, 88% yield) was then subjected to demethylation.

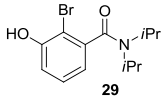
General procedure for the demethylation of 3-methoxy-benzamides.[4] (Procedure A) Step 2: The crude material (1.0 equiv, 2.0 g, 8.5 mmol) was dissolved in dry CH_2Cl_2 (0.20 M, 42 mL), placed under a nitrogen atmosphere, and cooled to -78 °C. A 1.0 M solution of BBr_3 in dichloromethane (2.0 equiv, 16.9 mL) was added dropwise and the reaction was allowed to gradually warm to room temperature and stir overnight. The reaction was quenched with ice water, extracted with ethyl acetate, washed with brine, and dried over Na_2SO_4. Recrystallization twice from hot ethanol afforded 1.6 g (87% yield) of a white crystalline solid. **TLC** R_f 0.79 (1:1

Hexanes:EtOAc); **IR** (FT-ATR, cm^{-1}) 3242, 2977, 1606, 1578, 1456, 1350; **^{1}H NMR** (400 MHz, MeOD) δ 7.24 (t, *J* = 7.9 Hz, 1H), 6.83 (dd, *J* = 8.2, 2.4 Hz, 1H), 6.74 (d, *J* = 7.5 Hz, 1H), 6.71-6.66 (m, 1H), 3.88 (bs, 1H), 3.61 (bs, 1H), 1.51 (bs, 6H), 1.16 (bs, 6H); **^{13}C NMR** (125 MHz, MeOD) δ 173.4, 159.0, 140.9, 131.0, 117.2, 117.0, 113.2, 52.7, 47.1, 20.7; **LCMS** (ESI) *m/z* calc'd for $C_{13}H_{20}NO_2$ $[M+H]^+$ 222.1494, found 222.1471.



26

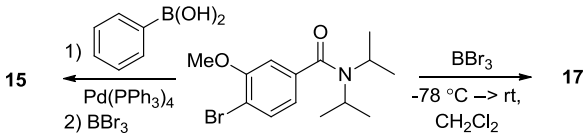
2-bromo-5-hydroxy-*N*,*N*-diisopropylbenzamide (26). Step 1: A flask was charged with *N*,*N*-diisopropyl-3-methoxybenzamide, synthesized as previously described (1.64 g, 6.97 mmol) and dissolved in dry CH_2Cl_2 (35 mL). Dibromodimethylhydantoin (DBDMH) (2.39 g, 8.40 mmol) was added, followed by dimethylacetamide (3.50 mL). The reaction was allowed to stir for 16 h at room temperature. The reaction was quenched with saturated sodium thiosulfate (exothermic). The organic layer was washed with water and dried with Na_2SO_4 to yield 2.07 g (95%) of a pale yellow solid. Step 2: Procedure A was followed with crude material (500 mg, 1.60 mmol), BBr_3 (3.2 mL, 3.2 mmol, 1.0 M) in dry CH_2Cl_2 (8.0 mL) at -78 °C. After stirring overnight at room temperature, the reaction was quenched with ice water. The organic layer was basified with 2 N NaOH and extracted. The aqueous layer was acidified with 1 N HCl and extracted with CH_2Cl_2. Organic layer was dried with Na_2SO_4 and concentrated. Material was recrystallized from hot EtOH/H_2O to yield two crops of pure white solids (328 mg, 68%). **TLC** R_f 0.27 (30% EtOAc/hexanes); **IR** (FT-ATR, cm^{-1}) 2973, 1611, 1589, 1459, 1349, 1291, 816; **^{1}H NMR** (500 MHz, MeOD) δ 7.39 (d, *J* = 8.7 Hz, 1H), 6.73 (dd, *J* = 8.7, 2.9 Hz, 1H), 6.64 (d, *J* = 2.9 Hz, 1H), 3.73-3.58 (m, 2H), 1.54 (d, *J* = 6.5 Hz, 3H), 1.53 (d, *J* = 6.5 Hz, 3H), 1.27 (d, *J* = 6.7 Hz, 3H), 1.12 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR** (125 MHz, MeOD) δ 170.5, 158.7, 141.4, 134.9, 118.6, 114.5, 108.0, 53.1, 47.3, 20.8, 20.7, 20.6, 20.4; **LCMS** (ESI) *m/z* calc'd for $C_{13}H_{19}BrNO_2$ $[M+H]^+$ 300.0599, found 300.0638.

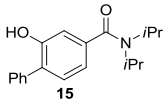


29

2-bromo-3-hydroxy-*N*,*N*-diisopropylbenzamide (29). Step 1: To a flame dried flask, *N*,*N*-diisopropyl-3-methoxybenzamide (2.00 g, 8.50 mmol) was added and dissolved in dry THF (85.0 mL, 0.1 M). The flask was then cooled to -78 ºC and *n*BuLi (3.89 mL, 9.34 mmol) was added dropwise over the course of ten minutes. Br_2 (1.30 mL, 25.5 mmol) was then slowly added dropwise to the reaction flask (exothermic). The reaction was allowed to stir for ten minutes at -78 ºC and then warmed to room temperature, diluted with ethyl acetate, and quenched with sat. $Na_2S_2O_3$. The organic layer was dried over Na_2SO_4 and concentrated to afford a pale yellow solid. Step 2: Procedure A was followed with the crude material, BBr_3 (17.0 mL, 17.0 mmol, 1.0 M) in dry CH_2Cl_2 (42.5 mL) at -78 °C. After stirring for 6 h at room temperature, the reaction was quenched with ice water and extracted with ethyl acetate. The organic layer was washed with brine and was dried with Na_2SO_4 and concentrated. Material was precipitated from hot ethyl acetate/hexanes to yield an off white solid (1.65 g, 65% over two steps). **TLC** R_f 0.23 (2.5% methanol/dichloromethane); **IR** (FT-ATR, cm^{-1}) 2925, 1606, 1566, 1446, 1349; **^{1}H NMR** (500 MHz, MeOD) δ 7.29-7.16 (m, 1H), 6.90 (dd, *J* = 8.2, 1.4 Hz, 1H),

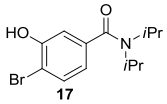
6.69 (dd, *J* = 7.5, 1.4 Hz, 1H), 3.74-3.56 (m, 2H), 1.56 (d, *J* = 6.8 Hz, 3H), 1.54 (d, *J* = 6.8 Hz, 3H), 1.26 (d, *J* = 6.7 Hz, 3H), 1.10 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR** (125 MHz, MeOD) δ 170.9, 156.2, 142.2, 130.0, 118.1, 116.9, 107.5, 53.1, 47.3, 20.8, 20.7, 20.6, 20.4; **LCMS** (ESI) *m/z* calc'd for $C_{13}H_{19}BrNO_2$ $[M+H]^+$ 300.0599, found 300.0605.





15

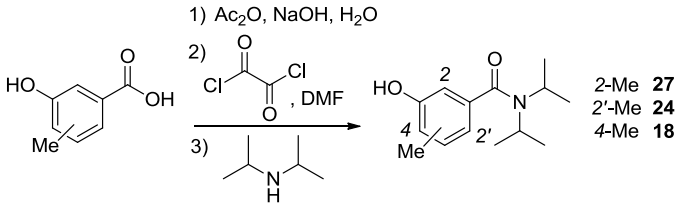
2-hydroxy-*N,N*-diisopropyl-[1,1'-biphenyl]-4-carboxamide (15). Step 1: A two-neck flask was charged with commercially available 4-bromo-*N,N*-diisopropyl-3-methoxybenzamide (Santa Cruz Biotech) (1.00 g, 3.20 mmol) and phenylboronic acid (582 mg, 4.80 mmol). $Pd(PPh_3)_4$ (370 mg, 0.32 mmol) was added, and the reaction headspace was purged and filled with nitrogen (3x). Degassed THF was introduced (32 mL), followed by 2M Na_2CO_3 (12.8 mL, 25.6 mmol) and the system was heated at 100 ºC, under reflux, overnight. The reaction was cooled to room temperature and diluted with EtOAc. The organics were washed with brine and dried with Na_2SO_4. The material was chromatographed in 10-50% ethyl acetate/hexanes to obtain an orange foam. Step 2: Material was subjected to demethylation (Procedure A) with BBr_3 (6.4 mL, 6.40 mmol, 1M) in CH_2Cl_2 (16 mL) overnight. After work up, material was purified by reverse phase chromatography using a Biotage SP4 system with a KP-C18-HS column (20% acetonitrile/water to 80% acetonitrile/water; flow rate = 40 mL/min) to yield a white powder (628 mg, 66% over two steps). **TLC** R_f 0.26 (30% EtOAc/hexanes); **IR** (FT-ATR, cm^{-1}) 2969, 1596, 1457, 1447, 1406, 1347; **^{1}H NMR** (500 MHz, MeOD) 7.60-7.52 (m, 2H), 7.39 (t, *J* = 7.7 Hz, 2H), 7.32 (t, *J* = 7.8 Hz, 2H), 6.86-6.81 (m, 1H), 6.83 (s, 1H), 3.99 (bs, 1H), 3.71-3.56 (m, 1H), 1.54 (bs, 6H), 1-37-1.01 (m, 6H); **^{13}C NMR** (125 MHz, MeOD) δ 173.3, 155.9, 139.7, 139.5, 132.1, 130.9, 130.3, 129.0, 128.0, 117.7, 114.0, 52.8, 47.2, 20.8; **LCMS** (ESI) *m/z* calc'd for $C_{19}H_{24}NO_2$ $[M+H]^+$ 298.1807, found 298.1773.



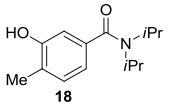
17

4-bromo-3-hydroxy-*N,N*-diisopropylbenzamide (17). Procedure A was followed with 4-bromo-*N,N*-diisopropyl-3-methoxybenzamide, BBr_3 (16.0 mL, 16.0 mmol, 1.0 M in hexanes) and CH_2Cl_2 (80.0 mL). The reaction was stirred at room temperature for 6 h, then quenched with ice water, extracted with EtOAc, and concentrated. Recrystallization from hot $EtOH/H_2O$ yielded a cream colored crystalline solid (2.17 g, 90%). **TLC** R_f 0.35 (30% EtOAc/hexanes); **IR** (FT- ATR, cm^{-1}) 2971, 1606, 1579, 1459, 1410, 1372, 1346, 1035; **^{1}H NMR** (500 MHz, MeOD) δ 7.52 (d, *J* = 8.0 Hz, 1H), 6.81 (d, *J* = 1.9 Hz, 1H), 6.68 (dd, *J* = 8.0, 1.9 Hz, 1H), 3.85 (bs, 1H), 3.61 (bs, 1H), 1.50 (bs, 6H), 1.16 (bs, 6H); **^{13}C NMR** (125 MHz,

MeOD) δ 169.3, 152.8, 137.0, 131.7, 115.6, 111.1, 108.7, 49.8, 44.2, 17.7; **LCMS** (ESI) *m/z* calc'd for $C_{13}H_{19}BrNO_2$ $[M+H]^+$ 300.0599, found 300.0596.

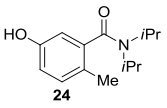


General synthesis of methyl- analogs of hydroxy-*N,N*-diisopropylbenzamide (Procedure B). Step 1:[5] To a flask containing sodium hydroxide (2.0 equiv) dissolved in water (0.9 M, in substrate) was added the benzoic acid (1.0 equiv). The reaction was cooled to 0 ºC and acetic anhydride (2.3 equiv) was added. Upon addition, the reaction was stirred at room temperature until completion, as monitored by TLC. The precipitate was filtered, washed with ice water, dried under high vacuum, and carried on crude. Step 2: Material was suspended in dry dichloromethane (0.05 M) and oxalyl chloride (1.1 equiv) was added at room temperature, followed by a catalytic amount (~1 mol%) of dimethylformamide. Acyl chloride formation was monitored by TLC and upon completion, the reaction was sparged with a vigorous stream of nitrogen. Step 3: The reaction vessel was cooled to 0 ºC and excess diisopropyl amine (7.0 equiv) was added dropwise. Upon completion, the reaction was stripped of CH_2Cl_2 under reduced pressure, and an equal volume of a methanol:saturated $NaHCO_3$ solution was added to facilitate acyl group deprotection. When complete, the reaction was diluted with ethyl acetate and acidified with 1 N HCl. Organic layer was dried with Na_2SO_4 and concentrated to yield solids that could be recrystallized to afford clean material.



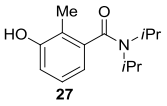
18

3-hydroxy-*N,N*-diisopropyl-4-methylbenzamide (18). Procedure B was followed using 3-hydroxy-4-methylbenzoic acid (1.66 g, 10.9 mmol), sodium hydroxide (960 mg, 24.0 mmol), and acetic anhydride (2.58 mL, 27.3 mmol) in water (12.0 mL) to afford the crude product. The material was carried on to acyl chloride formation with oxalyl chloride (1.10 mL, 12.0 mmol) and catalytic DMF in CH_2Cl_2 (200 mL). After removing excess HCl, the reaction was cooled, diisopropyl amine added (8.40 mL, 60.0 mmol), and stirred for 12 h. The flask was stripped of dichloromethane under rotary evaporation, and a methanol:saturated $NaHCO_3$ solution was added (100 mL, ~1:1). Upon workup, the crude product was recrystallized from hot EtOH:H_2O to afford a white powder (1.74 g, 82%). **TLC** R_f 0.35 (30% EtOAc/hexanes); **IR** (FT-ATR, cm^{-1}) 2970, 160, 1579, 1457, 1347; **^{1}H NMR** (500 MHz, MeOD) δ 7.11 (d, *J* = 7.4 Hz, 1H), 6.67 (d, *J* = 1.3 Hz, 1H), 6.65 (dd, *J* = 7.5, 1.5 Hz, 1H), 3.91 (bs, 1H), 3.60 (bs, 1H), 2.20 (s, 3H), 1.50 (bs, 6H), 1.16 (bs, 6H); **^{13}C NMR** (125 MHz, MeOD) δ 173.7, 156.8, 138.2, 132.0, 127.0, 117.2, 112.5, 52.6, 47.1, 20.8, 16.1; **LCMS** (ESI) *m/z* calc'd for $C_{14}H_{22}NO_2$ $[M+H]^+$ 236.1650, found 236.1667.



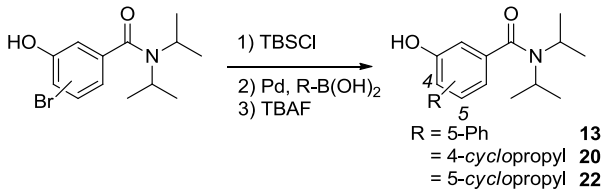
24

5-hydroxy-*N*,*N*-diisopropyl-2-methylbenzamide (24). Procedure B was followed using 5-hydroxy-2-methylbenzoic acid (592 mg, 3.90 mmol), sodium hydroxide (344mg, 8.60 mmol), and acetic anhydride (0.95 mL, 9.00 mmol) in water (4.3 mL) to afford the crude product. The material was carried on to acyl chloride formation with oxalyl chloride (0.33 mL, 3.70 mmol) and catalytic DMF in CH_2Cl_2 (74 mL). After removing excess HCl, the reaction was cooled, diisopropyl amine added (2.60 mL, 18.5 mmol), and stirred for 12 h. The flask was stripped of dichloromethane under rotary evaporation, and a methanol:saturated $NaHCO_3$ solution was added (50 mL, ~1:1). Upon workup, the crude product was recrystallized from hot EtOH:H_2O to afford two crops of white solids (558 mg, 74%). **TLC** R_f 0.29 (30% EtOAc/hexanes); **IR** (FT-ATR, cm^{-1}) 2970, 1600, 1577, 1462, 1347; **^{1}H NMR** (500 MHz, MeOD) δ 7.06 (d, *J* = 8.3 Hz, 1H), 6.71 (dd, *J* = 8.3, 2.5 Hz, 1H), 6.53 (d, *J* = 2.4 Hz, 1H), 3.77-3.67 (m, 1H), 3.67-3.56 (m, 1H), 2.19 (s, 3H), 1.54 (d, *J* = 6.8 Hz, 6H), 1.17 (d, *J* = 6.7 Hz, 3H), 1.13 (d, *J* = 6.7 Hz, 3H) ; **^{13}C NMR** (125 MHz, MeOD) δ 173.2, 156.7, 139.9, 132.7, 124.9, 116.7, 112.3, 52.7, 47.1, 20.8, 20.7, 17.9; **LCMS** (ESI) *m/z* calc'd for $C_{14}H_{22}NO_2$ $[M+H]^+$ 236.1650, found 236.1635.

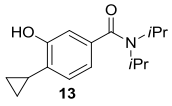


27

3-hydroxy-*N*,*N*-diisopropyl-2-methylbenzamide (27). Procedure B was followed using 3-hydroxy-2-methylbenzoic acid (1.66 g, 10.9 mmol), sodium hydroxide (960 mg, 24.0 mmol), and acetic anhydride (2.58 mL, 27.3 mmol) in water (12.0 mL) to afford 1.71 g of a pinkish crude product. The material was carried on to acyl chloride formation with oxalyl chloride (0.84 mL, 9.7 mmol) and catalytic DMF in CH_2Cl_2 (175 mL, 0.5 M). After removing excess HCl, the reaction was cooled, diisopropyl amine added (8.40 mL, 60.0 mmol), and stirred for 12 h. The flask was stripped of dichloromethane under rotary evaporation, and a methanol:saturated $NaHCO_3$ solution was added (100 mL, ~1:1). Upon workup, the crude product was recrystallized from hot EtOH:H_2O to afford a white crystalline solid (1.31 g, 62%). **TLC** R_f 0.26 (30% EtOAc/hexanes); **IR** (FT-ATR, cm^{-1}) 3273, 2971, 2438, 1604, 1583, 1372, 1348; **^{1}H NMR** (500 MHz, MeOD) 7.05 (t, *J* = 7.8 Hz, 1H), 6.77 (d, *J* = 8.1 Hz, 1H), 6.58 (d, *J* = 7.5 Hz, 1H), 3.76-3.67 (m, 1H), 3.67-3.57 (m, 1H), 2.13 (s, 3H), 1.56 (d, *J* = 6.8 Hz, 3H), 1.54 (d, *J* = 6.9 Hz, 3H), 1.16 (d, *J* = 6.7 Hz, 3H), 1.11 (d, *J* = 6.7 Hz, 3H) ; **^{13}C NMR** (125 MHz, MeOD) δ 173.4, 157.3, 140.6, 128.0, 121.4, 116.6, 115.7, 52.7, 47.1, 20.8, 20.8, 20.7, 20.7, 12.8; **LCMS** (ESI) *m/z* calc'd for $C_{14}H_{22}NO_2$ $[M+H]^+$ 236.1650, found 236.1637.



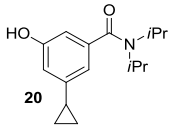
General synthesis of phenyl- and cyclopropyl- analogs of 3-hydroxy-*N*,*N*-diisopropylbenzamide (Procedure C). Step 1: Following procedure A or B, the respective mono-bromo-3-hydroxy-*N*,*N*-diisopropylbenzamide were synthesized (e.g. **17**). Step 2: The hydroxy- compound (1.0 equiv) was placed into a flame dried flask with *tert*-butylchlorodimethylsilane (TBSCl) (1.2 equiv), followed by dry dichloromethane (0.5M), dimethylaminopyridine (DMAP) (0.1 equiv), and triethylamine (1.5 equiv).[6] The reaction was stirred at room temperature for 1 h. The reaction was quenched by the addition of water and CH_2Cl_2 was extracted. The organic layer was washed with 1N HCl and brine, dried over Na_2SO_4 and carried on crude. Step 2: The residue (1.0 equiv) was placed into a two-neck flask with the corresponding boronic acid (2.0-3.0 equiv), potassium phosphate (K_3PO_4) (6.0 equiv), and palladium tetrakis ($Pd(PPh_3)_4$) (0.1 equiv). A reflux condenser was attached and the system was filled with nitrogen and evacuated (3x). The solvent system, toluene:H_2O, (20:1, 0.1 M) was degassed and transferred to the reaction vessel. The reaction was heated at 95 ºC until completion, as monitored by LC/MS. The reaction was allowed to cool to room temperature and diluted with ethyl acetate. The mixture was washed with water and organics were dried over Na_2SO_4 and concentrated. The material was purified by flash chromatography with ethyl acetate/hexanes. Step 3: Silyl group deprotection with tetrabutylammoniumfluoride (TBAF) (1.2 equiv) in THF (0.075 M) for 1 h afforded product. The reaction was washed with 1N HCl and extracted with ethyl acetate. The organic layer was washed with brine and dried with Na_2SO_4. Upon concentration, the material was purified by reverse phase column chromatography using a Biotage SP4 system with a KP-C18-HS column (10% acetonitrile/water to 90% acetonitrile/water; flow rate = 45 mL/min).



13

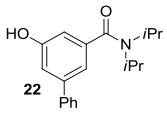
4-cyclopropyl-3-hydroxy-*N*,*N*-diisopropylbenzamide (13). Following procedure A, 4-bromo-3-hydroxy-*N*,*N*-diisopropylbenzamide (1.50 g, 5.00 mmol) was obtained. Step 2: Following procedure C, this material was suspended in CH_2Cl_2 (10 mL) with TBSCl (829 mg, 5.50 mmol), DMAP (61.2 mg, 0.50 mmol), and NEt_3 (1.00 mL, 7.50 mmol). Upon work up, a crude viscous oil was obtained (1.86 g, 90%). Step 3: This material (4-bromo-3-((*tert*-butyldimethylsilyl)oxy)-*N*,*N*-diisopropylbenzamide) (725 mg, 1.74 mmol), cyclopropylboronic acid (451 mg, 5.25 mmol), $Pd(PPh_3)_4$ (201 mg, 0.174 mmol) and K_3PO_4 (1.39 g, 10.4 mmol) were added and the flask headspace was purged and filled with nitrogen (3x). Degassed toluene:H_2O were introduced (17.4 mL, 20:1) and the reaction was heated at 95 ºC for 4 h. The material, after work up, was chromatographed in 10% ethyl acetate/hexanes. Step 4: The residue was dissolved in THF (23 mL, 0.075 M) and TBAF (2.1 mL, 2.08 mmol, 1M) was added and allowed to stir for 1 hr. After work up, the material was purified by reverse phase

chromatography to afford a pale cream powder (260 mg, 57% over two steps). **TLC** R_f 0.29 (30% EtOAc/hexanes); **IR** (FT-ATR, cm^{-1}) 3293, 2970, 1599, 1569, 1457, 1347; **^{1}H NMR** (500 MHz, MeOD) 6.85 (d, *J* = 7.6 Hz, 1H), 6.70-6.64 (m, 2H), 3.91 (bs, 1H), 3.60 (bs, 1H), 2.16-2.06 (m, 1H), 1.50 (bs, 6H), 1.09 (bs, 6H), 0.96-0.86 (m, 2H), 0.69-0.58 (m, 2H); **^{13}C NMR** (125 MHz, MeOD) δ 173.6, 157.3, 137.4, 132.5, 126.5, 117.4, 112.6, 52.7, 47.0, 20.8, 10.3, 8.0; **LCMS** (ESI) *m/z* calc'd for $C_{16}H_{24}NO_2$ $[M+H]^+$ 262.1807, found 262.1830.



20

3-cyclopropyl-5-hydroxy-*N*,*N*-diisopropylbenzamide (20). Following procedure B, 3-bromo-5-hydroxy-*N*,*N*-diisopropylbenzamide (3.69 g, 12.3 mmol) was obtained. Following procedure C, Step 2: This material was suspended in CH_2Cl_2 (24.6 mL) with TBSCl (2.00 g, 13.5 mmol), DMAP (150 mg, 1.23 mmol), and NEt_3 (2.50 mL, 18.4 mmol). Upon work up, a crude sticky white foam was obtained (3.65 g, 72%). Step 3: A two-neck flask was charged with this material (3-bromo-5-((tert-butyldimethylsilyl)oxy)-N,N-diisopropylbenzamide) (1.50 g, 3.60 mmol), cyclopropylboronic acid (933 mg, 10.8 mmol), $Pd(PPh_3)_4$ (416 mg, 0.36 mmol) and K_3PO_4 (2.89 g, 21.6 mmol). The flask purged with nitrogen, degassed toluene:H_2O were introduced (36.0 mL, 20:1), and the reaction was heated at 95 ºC for 3 h. The material, after work up, was chromatographed in 20% ethyl acetate/ hexanes yielding a crude yellow oil. Step 4: The residue was dissolved in THF (48 mL, 0.075 M) and TBAF (4.80 mL, 4.30 mmol, 1M) was added and allowed to stir for 1 hr. After work up, the material was purified by reverse phase chromatography to afford a white foam (564 mg, 60% over two steps). **TLC** R_f 0.26 (30% EtOAc/hexanes); **IR** (FT-ATR, cm^{-1}) 2970, 1586, 1437, 1371, 1344, 1157; **^{1}H NMR** (500 MHz, MeOD) 6.54-6.50 (m, 1H), 6.47-6.44 (m, 2H), 3.86 (bs, 1H), 3.59 (bs, 1H), 1.91-1.81 (m, 1H), 1.50 (bs, 6H), 1.15 (bs, 6H), 1.00-0.91 (m, 2H), 0.71-0.66 (m, 2H); **^{13}C NMR** (125 MHz, MeOD) δ 173.6, 158.9, 148.1, 140.7, 114.7, 113.8, 110.2, 52.7, 47.1, 20.7, 16.1, 9.8; **LCMS** (ESI) *m/z* calc'd for $C_{16}H_{24}NO_2$ $[M+H]^+$ 262.1807, found 262.1788.



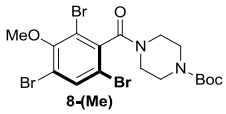
22

5-hydroxy-*N*,*N*-diisopropyl-[1,1'-biphenyl]-3-carboxamide (22). From Step 3 (see **20** for step 1 and 2): A two-neck flask was charged with this material (3-bromo-5-((*tert*-butyldimethylsilyl)oxy)-*N*,*N*-diisopropylbenzamide) (1.50 g, 3.60 mmol), phenylboronic acid (878 mg, 7.2 mmol), $Pd(PPh_3)_4$ (416 mg, 0.36 mmol), and K_3PO_4 (2.89 g, 21.6 mmol). Degassed toluene:H_2O was introduced (36.0 mL, 20:1) and the reaction was refluxed under nitrogen at 95 ºC overnight. The material, after work up, was chromatographed in 10-20% ethyl acetate/hexanes. Step 4: The residue was dissolved in THF (48 mL, 0.075 M), TBAF (4.80 mL, 4.30 mmol, 1M) was added, and allowed to stir for 1 hr. After work up, the material was purified by reverse phase chromatography to afford a pale cream powder (575 mg, 54% over two steps). **TLC** R_f 0.23 (30% EtOAc/hexanes); **IR** (FT-ATR, cm^{-1}) 2970, 1597, 1580, 1458, 1406, 1348; **^{1}H NMR** (500 MHz, MeOD) 7.65-7.54 (m, 2H), 7.45-7.50 (m, 2H), 7.39-7.28 (m, 1H),

7.09-7.04 (m, 1H), 6.97 (t, *J* = 1.5 Hz, 1H), 6.69 (dd, *J* = 2.2, 1.4 Hz, 1H), 3.96 (bs, 1H), 3.64 (bs, 1H), 1.54 (bs, 6H), 1.20 (bs, 6H); **^{13}C NMR** (125 MHz, MeOD) δ 173.3, 159.4, 144.7, 141.6, 141.3, 129.9, 128.8, 128.0, 116.0, 115.5, 112.2, 52.8, 47.2, 20.8; **LCMS** (ESI) *m/z* calc'd for $C_{19}H_{24}NO_2$ $[M+H]^+$ 298.1807, found 298.1786.

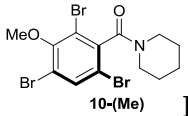
IV. General Synthesis of di- and tri-Brominated *N,N*-dialkyl Amides (Procedure D).

Dibromodimethylhydantoin (DBDMH, 1.0-1.5 equiv) was added to a 0.02 M solution of the aromatic amide (0.20 mmol, 1 equiv) and catalyst **6** (11.5 mg, 0.02 mmol, 0.1 equiv) in $CHCl_3$ (10 mL) at -40 ºC. The reaction was allowed to stir until reaction completion (8-48 h). The reaction was then quenched with a 1.5 M solution of butyl vinyl ether in methanol (0.5 mL). The reaction was allowed to warm to room temperature and additional methanol was added (2.0 mL, ~5:1 by volume DCM:MeOH) followed by 2.0 M trimethylsilyldiazomethane in hexanes (4.0 equiv). The methylation was monitored by TLC and was quenched with silica gel upon completion (15 min-2 h). The reaction was filtered and concentrated under reduced pressure. Flash chromatrography of the crude residue with hexanes/ethyl acetate afforded product. Data from the results of three experiments are reported.



8-(Me)

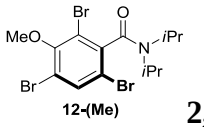
***tert*-butyl-4-(2,4,6-tribromo-3-methoxybenzoyl)piperazine-1-carboxylate (8-(Me)).** Procedure D was followed using **7** (61.3 mg) and DBDMH (85.8 mg, 0.30 mmol) for 20-40 h. The product was purified by flash chromatography (10-30% ethyl acetate/hexanes) to afford product as a white solid. Yield 1: 87.3 mg, 78%; yield 2: 93.6 mg, 84%; yield 3: 105.4 mg, 95%; **HPLC** 75:25 er (Chiralcel OD-H, 0.75 mL/min, 97:3 hexanes:ethanol): $R_{T(Minor)}$ = 18.9 min, $R_{T(Major)}$ = 20.7 min; $[\alpha]_D^{20.0}$ -7.5 (*c* 1.0, $CHCl_3$); **TLC** R_f 0.21 (10% hexanes/ethyl acetate); **IR** (FT-ATR, cm^{-1}) 2976, 1694, 1649, 1408, 1239, 1165; **^{1}H NMR** (500 MHz, MeOD) δ 7.99 (s, 1H), 3.92 (s, 3H), 3.85-3.71 (m, 2H), 3.60 (bs, 2H), 3.56-3.48 (m, 2H), 3.32-3.26 (m, 2H), 1.49 (s, 9H); **^{13}C NMR** (125 MHz, MeOD) δ 166.8, 156.0, 155.9, 140.5, 137.4, 120.2, 117.4, 115.5, 81.8, 61.4, 47.2, 42.5, 28.6; **LCMS** (ESI) *m/z* calc'd for $C_{17}H_{22}Br_3N_2O_4$ $[M+H]^+$ 554.9129, found 554.9102.



10-(Me)

Piperidin-1-yl(2,4,6-tribromo-3-methoxyphenyl)methanone (10-(Me)). Procedure D was followed using **9** (41.0 mg) and DBDMH (85.8 mg, 0.30 mmol) for 4-20 h. The product was purified by flash chromatography (20% ethyl acetate/hexanes) to afford product as a white solid. Yield 1: 79.5 mg, 87%; yield 2: 82.7 mg, 91%; yield 3: 89.7 mg, 99%; **HPLC** 90:10 er (Chiralpak AD-H, 1.0 mL/min, 95:5 hexanes:ethanol): $R_{T(Minor)}$ = 8.8 min, $R_{T(Major)}$ = 11.1 min; $[\alpha]_D^{20.0}$ -13.6 (*c* 1.0, $CHCl_3$); **TLC** R_f 0.35 (10% hexanes/ethyl acetate); **IR** (FT-ATR, cm^{-1}) 2936, 1634, 1444, 1344, 1269, 994; **^{1}H NMR** (500 MHz, MeOD) δ 7.95 (s, 1H),

3.90 (s, 3H), 3.79-3.67 (m, 2H), 3.27-3.19 (m, 2H), 1.76-1.69 (m, 4H), 1.68-1.62 (m, 2H); **^{13}C NMR** (125 MHz, MeOD) δ 166.4, 155.8, 141.2, 137.3, 119.8, 117.4, 115.5, 61.3, 43.6, 27.2, 26.3, 25.3; **LCMS** (ESI) *m/z* calc'd for $C_{13}H_{15}Br_3NO_2$ $[M+H]^+$ 453.8653, found 453.8683.



12-(Me)

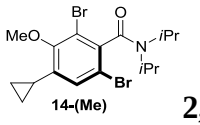
2,4,6-tribromo-*N,N*-diisopropyl-3-methoxybenzamide (12-(Me)). Procedure D was followed using **11** (44.3 mg) and DBDMH (85.8 mg, 0.30 mmol) for 8-20 h. The product was purified by flash chromatography (20% ethyl acetate/hexanes) to afford product as a white solid. Yield 1: 80.3 mg, 85%; yield 2: 84 mg, 89%; yield 3: 88.4 mg, 94%; **HPLC** 94:6 er (Chiralpak AD-H, 1.0 mL/min, 95:5 hexanes:ethanol): $R_{T(Minor)}$ = 5.4 min, $R_{T(Major)}$ = 7.0 min; $[\alpha]_D^{20.0}$ -12.4 (*c* 1.0, $CHCl_3$); **TLC** R_f 0.56 (20% ethyl acetate/hexanes); **IR** (FT-ATR, cm^{-1}) 2979, 1637, 1446, 1320, 1014; **^{1}H NMR** (500 MHz, MeOD) δ 7.93 (s, 1H), 3.88 (s, 3H), 3.75-3.64 (m, 1H), 3.59 (hept, *J* = 6.6 Hz, 1H), 1.58 (d, *J* = 6.9 Hz, 3H), 1.57 (d, *J* = 6.7 Hz, 3H), 1.28 (d, *J* = 6.7 Hz, 3H), 1.28 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR** (125 MHz, MeOD) δ 167.2, 155.8, 141.9, 137.4, 119.3, 117.4, 115.4, 61.3, 53.7, 48.0, 21.0, 21.0, 20.3, 20.3; **LCMS** (ESI) *m/z* calc'd for $C_{14}H_{19}Br_3NO_2$ $[M+H]^+$ 469.8966, found 469.9014. Crystals for X-ray spectroscopy grown from benzene/pentane vapor diffusion and provided an absolute configuration assignment of the major enantiomer as ***aS*** (or ***P***).

Note: Absolute configuration of all other atropisomeric compounds assigned by analogy to **12**.

Procedure D was also followed using **17** (60.0 mg) and DBDMH (57.2 mg, 0.20 mmol) for 14-19 h. The product was purified by flash chromatography (20% ethyl acetate/hexanes) to afford **12-(Me)** as a white solid. Yield 1: 86 mg, 91%; yield 2: 83.1 mg, 88%; yield 3: 84.2 mg, 89%; **HPLC** 92:8 er.

Procedure D was also followed using **26** (60.0 mg) and DBDMH (57.2 mg, 0.20 mmol) for 18-24 h. The product was purified by flash chromatography (20% ethyl acetate/hexanes) to afford **12-(Me)** as a white solid. Yield 1: 86 mg, 91%; yield 2: 86.3 mg, 91%; yield 3: 83.3 mg, 88%; **HPLC** 52:48 er.

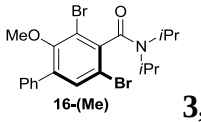
Procedure D was also followed using **29** (60.0 mg) and DBDMH (57.2 mg, 0.20 mmol) for 21-72 h. The product was purified by flash chromatography (20% ethyl acetate/hexanes) to afford **12-(Me)** as a white solid. Yield 1: 77.4 mg, 82%; yield 2: 73.4 mg, 78%; yield 3: 61.6 mg, 65% (72 h), yield 4: 71.0 mg, 75%; **HPLC** 51:49 er.



14-(Me)

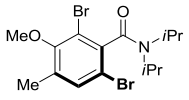
2,6-dibromo-*N,N*-diisopropyl-3-methoxy-4-methylbenzamide (14-(Me)). Procedure D was followed using **13** (52.3 mg) and DBDMH (57.2 mg, 0.20 mmol) for 24-48 h.

The product was purified by flash chromatography (20% ethyl acetate/hexanes) to afford product as a white solid. Yield 1: 65 mg, 75%; yield 2: 68 mg, 79%; yield 3: 71.5 mg, 83%; **HPLC** 96:4 er (Chiralpak AD-H, 1.0 mL/min, 95:5 hexanes:ethanol): $R_{T(Minor)}$ = 5.3 min, $R_{T(Major)}$ = 6.8 min; $[\alpha]_D^{20.0}$ -13.5 (*c* 1.0, $CHCl_3$); **TLC** R_f 0.54 (20% hexanes/ethyl acetate); **IR** (FT-ATR, cm^{-1}) 2967, 1637, 1445, 1365, 1328, 1019; **^{1}H NMR** (500 MHz, MeOD) δ 7.07 (s, 1H), 3.87 (s, 3H), 3.71-3.63 (m, 1H), 3.64-3.54 (m, 1H), 2.22 (tt, *J* = 8.5, 5.3 Hz, 1H), 1.58 (d, *J* = 6.7 Hz, 3H), 1.57 (d, *J* = 6.7 Hz, 3H), 1.27 (d, *J* = 6.7 Hz, 3H), 1.26 (d, *J* = 6.7 Hz, 3H), 1.16-0.98 (m, 2H), 0.82-0.64 (m, 2H); **^{13}C NMR** (125 MHz, MeOD) δ 168.1, 157.2, 142.2, 139.1, 129.4, 116.5, 115.2, 61.4, 53.6, 47.8, 21.0, 20.4, 20.4, 10.8, 10.0, 9.8; **LCMS** (ESI) *m/z* calc'd for $C_{17}H_{24}Br_2NO_2$ $[M+H]^+$ 432.0174, found 432.0209.



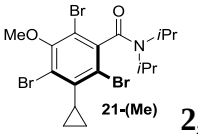
16-(Me)

3,5-dibromo-*N*,*N*-diisopropyl-2-methoxy-[1,1'-biphenyl]-4-carboxamide (16-(Me)). Procedure D was followed using **15** (59.5 mg) and DBDMH (57.2 mg, 0.20 mmol) for 5-14 h. The product was purified by flash chromatography (20% ethyl acetate/hexanes) to afford product as a white solid. Yield 1: 88 mg, 94%; yield 2: 80.0 mg, 72%; yield 3: 75.2 mg, 80%; **HPLC** 93:7 er (Chiralpak AD-H, 1.0 mL/min, 95:5 hexanes:ethanol): $R_{T(Minor)}$ = 5.2 min, $R_{T(Major)}$ = 6.4 min; $[\alpha]_D^{20.0}$ -9.0 (*c* 1.0, $CHCl_3$); **TLC** R_f 0.42 (10% hexanes/ethyl acetate); **IR** (FT-ATR, cm^{-1}) 2972, 2932, 1640, 1444, 1360, 1329; **^{1}H NMR** (500 MHz, MeOD) δ 7.61 (s, 1H), 7.96-7.53 (m, 2H), 7.50-7.44 (m, 2H), 7.44-7.39 (m, 1H), 3.76-3.64 (m, 2H), 3.42 (s, 3H), 1.61 (d, *J* = 6.8 Hz, 3H), 1.60 (d, *J* = 6.8 Hz, 3H), 1.31 (d, *J* = 6.6 Hz, 6H); **^{13}C NMR** (125 MHz, MeOD) δ 167.8, 155.8, 141.2, 139.1, 137.2, 135.3, 130.0, 129.7, 129.6, 117.4, 115.0, 61.0, 53.7, 47.9, 21.1, 21.0, 20.4, 20.4; **LCMS** (ESI) *m/z* calc'd for $C_{20}H_{24}Br_2NO_2$ $[M+H]^+$ 468.0174, found 468.0642.



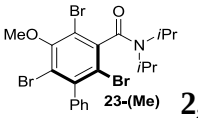
19-(Me)

2,6-dibromo-*N*,*N*-diisopropyl-3-methoxy-4-methylbenzamide (19-(Me)). Procedure D was followed using **18** (47.0 mg) and DBDMH (57.2 mg, 0.20 mmol) for 48 h. The product was purified by flash chromatography (20% ethyl acetate/hexanes) to afford product as a white solid. Yield 1: 51.2 mg, 63%; yield 2: 55 mg, 68%; yield 3: 60.8 mg, 75%; **HPLC** 93:7 er (Chiralpak AD-H, 1.0 mL/min, 95:5 hexanes:ethanol): $R_{T(Minor)}$ = 5.1 min, $R_{T(Major)}$ = 6.3 min; $[\alpha]_D^{20.0}$ -21.3 (*c* 1.0, $CHCl_3$); **TLC** R_f 0.39 (10% hexanes/ethyl acetate); **IR** (FT-ATR, cm^{-1}) 2973, 2935, 1640, 1446, 1359, 1326, 1018; **^{1}H NMR** (500 MHz, MeOD) δ 7.50 (s, 1H), 3.80 (s, 3H), 3.67 (dq, *J* = 13.4, 6.8 Hz, 1H), 3.59 (dq, *J* = 12.9, 6.5 Hz, 1H), 2.33 (s, 3H), 1.58 (d, *J* = 6.8 Hz, 3H), 1.57 (d, *J* = 6.8 Hz, 3H), 1.27 (d, *J* = 6.6 Hz, 6H); **^{13}C NMR** (125 MHz, MeOD) δ 168.0, 156.8, 139.9, 136.3, 135.6, 116.4, 114.7, 60.8, 53.6, 47.8, 21.0, 21.0, 20.4, 20.4, 16.4; **LCMS** (ESI) *m/z* calc'd for $C_{15}H_{22}Br_2NO_2$ $[M+H]^+$ 406.0017, found 406.0040.



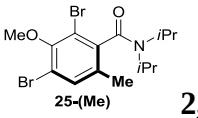
21-(Me)

2,4,6-tribromo-3-cyclopropyl-*N*,*N*-diisopropyl-5-methoxybenzamide (21-(Me)). Procedure D was followed using **20** (52.3 mg) and DBDMH (85.8 mg, 0.30 mmol) for 3-9 h. The product was purified by flash chromatography (20% ethyl acetate/hexanes) to afford product as a white solid. Yield 1: 86 mg, 84%; yield 2: 95 mg, 93%; yield 3: 93.8, 92%; **HPLC** 92:8 er (Chiralpak IC, 1.0 mL/min, 90:10 hexanes:ethanol): $R_{T(Major)}$ = 9.7 min, $R_{T(Minor)}$ = 10.7 min; $[\alpha]_D^{20.0}$ -2.3 (*c* 1.0, $CHCl_3$); **TLC** R_f 0.48 (10% hexanes/ethyl acetate); **IR** (FT-ATR, cm^{-1}) 2972, 2933, 1641, 1348, 1315; **^{1}H NMR** (500 MHz, MeOD) δ 3.86 (s, 3H), 3.73-3.65 (m, 1H), 3.56 (hept, *J* = 6.6 Hz, 1H), 1.79 (tt, *J* = 8.4, 5.8 Hz, 1H), 1.58 (d, *J* = 6.8 Hz, 6H), 1.33-1.28 (m, 2H), 1.28 (d, *J* = 6.6 Hz, 3H), 1.26 (d, *J* = 6.6 Hz, 3H), 0.78-0.70 (m, 2H); **^{13}C NMR** (125 MHz, MeOD) δ 167.8, 155.8, 144.4, 141.8, 124.9, 120.7, 114.8, 61.1, 53.6, 48.0, 21.0, 20.9, 20.3, 20.2, 20.2, 12.9, 12.7; **LCMS** (ESI) *m/z* calc'd for $C_{17}H_{23}Br_3NO_2$ $[M+H]^+$ 432.0174, found 432.0209.



23-(Me)

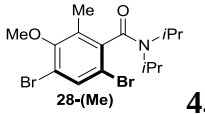
2,4,6-tribromo-*N*,*N*-diisopropyl-5-methoxy-[1,1'-biphenyl]-3-carboxamide (23-(Me)). Procedure D was followed using **22** (59.5 mg) and DBDMH (85.8 mg, 0.30 mmol) for 2-12 h. The product was purified by flash chromatography (20% ethyl acetate/hexanes) to afford product as a white solid. Yield 1: 89.0 mg, 81%; yield 2: 98.4 mg, 90%; yield 3: 106.3 mg, 97%; **HPLC** 93:7 er (Chiralpak IC, 1.0 mL/min, 97:3 hexanes:ethanol): $R_{T(Major)}$ = 22.9 min, $R_{T(Minor)}$ = 24.2 min; $[\alpha]_D^{20.0}$ +14.1 (*c* 1.0, $CHCl_3$); **TLC** R_f 0.45 (10% hexanes/ethyl acetate); **IR** (FT-ATR, cm^{-1}) 2973, 1641, 1444, 1343; **^{1}H NMR** (500 MHz, MeOD) δ 7.50-7.45 (m, 2H), 7.45-7.40 (m, 1H), 7.20-7.16 (m, 1H), 7.16-1.12 (m, 1H), 3.91 (s, 3H), 3.72-3.64 (m, 2H), 1.60 (d, *J* = 6.8 Hz, 3H), 1.55 (d, *J* = 6.8 Hz, 3H), 1.32 (d, *J* = 6.6 Hz, 3H), 1.29 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR** (125 MHz, MeOD) δ 167.6, 155.9, 146.6, 142.0, 141.9, 130.0, 130.0, 129.6, 129.5, 129.5, 121.4, 117.2, 116.0, 61.2, 53.7, 48.0, 21.1, 21.0, 20.3, 20.2; **LCMS** (ESI) *m/z* calc'd for $C_{20}H_{23}Br_3NO_2$ $[M+H]^+$ 545.9279, found 545.9338.



25-(Me)

2,4-dibromo-*N*,*N*-diisopropyl-3-methoxy-6-methylbenzamide (25-(Me)). Procedure D was followed using **24** (47.0 mg) and DBDMH (57.2 mg, 0.20 mmol) for 24-40 h. The product was purified by flash chromatography (20% ethyl acetate/hexanes) to afford product as a white solid. Yield 1: 71.2 mg, 87%; yield 2: 54.5 mg, 67%; yield 3: 70 mg, 86%; **HPLC** 90:10 er (Chiralpak AD-H, 1.0 mL/min, 95:5 hexanes:ethanol): $R_{T(Minor)}$ = 5.2 min, $R_{T(Major)}$ = 6.3 min; $[\alpha]_D^{20.0}$ -24.0 (*c* 1.0, $CHCl_3$); **TLC** R_f 0.40 (10% hexanes/ethyl acetate); **IR** (FT-ATR, cm^{-1}) 2971, 1635, 1440, 1378, 1327, 1021; **^{1}H NMR** (500 MHz, MeOD) δ 7.53 (s, 1H), 3.84 (s, 3H), 3.69 (hept, *J* = 6.8 Hz, 1H), 3.59 (hept, *J* = 6.7 Hz, 1H), 2.29 (s, 3H), 1.59 (d, *J* = 6.8 Hz,

3H), 1.56 (d, *J* = 6.8 Hz, 3H), 1.28 (d, *J* = 6.6 Hz, 3H), 1.17 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR** (125 MHz, MeOD) δ 169.0, 153.8, 140.9, 135.6, 134.1, 118.3, 116.1, 61.1, 53.3, 47.7, 21.2, 21.0, 20.6, 20.3, 18.8; **LCMS** (ESI) *m/z* calc'd for $C_{15}H_{22}Br_2NO_2$ $[M+H]^+$ 406.0017, found 406.0033.



28-(Me)

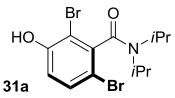
4,6-dibromo-*N*,*N*-diisopropyl-3-methoxy-2-methylbenzamide (28-(Me)). Procedure D was followed using **27** (47.0 mg) and DBDMH (57.2 mg, 0.20 mmol) for 24 h. The product was purified by flash chromatography (20% ethyl acetate/hexanes) to afford product as a white solid. Yield 1: 65 mg, 80%; yield 2: 50.2 mg, 62%; yield 3: 69 mg, 85%; **HPLC** 63:37 er (Chiralpak IC, 1.0 mL/min, 95:5 hexanes:ethanol): $R_{T(Major)}$ = 16.4 min, $R_{T(Minor)}$ = 17.8 min; **[α]** $^{20.0}_{D}$ +2.7 (*c* 1.0, $CHCl_3$); **TLC** R_f 0.34 (10% hexanes/ethyl acetate); **IR** (FT-ATR, cm^{-1}) 2971, 2935, 1635, 1446, 1383, 1370, 1329; **^{1}H NMR** (500 MHz, MeOD) δ 7.73 (s, 1H), 3.81 (s, 3H), 3.74-3.64 (m, 1H), 3.60 (hept, *J* = 6.6 Hz, 1H), 2.31 (s, 3H), 1.58 (d, *J* = 6.6 Hz, 3H), 1.57 (d, *J* = 6.8 Hz, 3H), 1.29 (d, *J* = 6.6 Hz, 3H), 1.17 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR** (125 MHz, MeOD) δ 169.0, 156.9, 140.8, 135.5, 132.7, 118.8, 114.7, 60.9, 53.4, 47.8, 21.1, 20.9, 20.6, 20.3, 14.5; **LCMS** (ESI) *m/z* calc'd for $C_{15}H_{22}Br_2NO_2$ $[M+H]^+$ 406.0017, found 406.0026.

V. Representative Mol-Scale Tribromination of 11 Followed by Recrystallization.

Dibromodimethylhydantoin (429 mg, 1.50 mmol) was added to a 0.02 M solution of **11** (221 mg, 1.00 mmol) and catalyst **6** (57.6 mg, 0.10 mmol) in $CHCl_3$ (50 mL) at -40 ºC. The reaction was allowed to stir until reaction completion (18 h). The reaction was then quenched with a 1.5 M solution of butyl vinyl ether in methanol (1.0 mL). The reaction was allowed to warm to room temperature and additional methanol was added (10 mL, ~5:1 by volume DCM: MeOH) followed by 2.0 M trimethylsilyldiazomethane in hexanes (1.5 mL, 3.0 mmol). The methylation was monitored by TLC and was quenched with silica gel upon completion. The reaction was filtered and concentrated under reduced pressure. The product was purified by silica gel flash chromatography (10% ethyl acetate/hexanes) to afford product as a white solid (447 mg, 95% yield, 95:5 er). The product was then recrystallized from ethanol:water to obtain a white crystalline solid (259 mg, 56% recovered enantioenriched, 98:2 er).

VI. Mechanism-Driven Studies of Reactions Run to Low Conversion (Scheme 1).

a. Preparation of Authentic Reaction Intermediate Sample.



31a

2,6-dibromo-3-hydroxy-*N*,*N*-diisopropylbenzamide (31a). Step 1: In a regioselective dehalogenation procedure adapted from Buchwald,[7] an oven-dried vial was charged with tribrominated biaryl **12-(Me)** (300.0 mg, 0.64 mmol), *rac*-BINAP (22.0 mg, 0.036 mmol), and $Pd(OAc)_2$ (7.2 mg, 0.030 mmol). The vial was purged with argon and degassed, anhydrous THF (1.30 mL) was added and reaction mixture was allowed to stir for five minutes.

TMEDA (0.14 mL, 0.96 mmol) and additional THF (1.30 mL) were added, and the reaction stirred for five minutes at room temperature. $NaBH_4$ (0.5M solution in anhydrous DMF, 1.34 mL, 0.67 mmol) was slowly added, and the reaction was allowed to stir at 50°C for 12 h under Ar. At this time, the reaction was allowed to cool, filtered through a pad of silica gel eluting with ethyl acetate and then concentrated under reduced pressure. Purification via reverse phase column chromatography using a Biotage SP4 system with a KP-C18-HS column (10% acetonitrile/water to 80% acetonitrile/water; flow rate = 40 mL/min) afforded mono-dehalogenated product (**31a-(Me)**) in good regioselectivity (7% impurity, 217 mg, 85% yield). Step 2: A portion of this material (30.0 mg, 0.08 mmol) was then carried on to demethylation utilizing Procedure A with BBr_3 (0.15 mL, 0.15 mmol, 1.0 M in hexanes) and CH_2Cl_2 (0.80 mL). The reaction was stirred at room temperature for 12 h, then quenched with ice water, extracted with EtOAc, and concentrated. Reverse phase column chromatography using a Biotage SP4 system with a KP-C18-HS column (0% acetonitrile/water to 80% acetonitrile/water; flow rate = 30 mL/min) afforded a clean sample of di-Br **31a**. **TLC** R_f 0.26 (2.5% Methanol/DCM); **IR** (FT-ATR, cm^{-1}) 2971, 1611, 1557, 1444, 1341, 1295, 819; **^{1}H NMR** (500 MHz, MeOD) δ 7.40 (d, *J* = 8.7, 1H), 6.83 (d, *J* = 8.7, 1H), 3.72-3.56 (m, 2H), 1.58 (d, *J* = 6.8, 3H), 1.57 (d, *J* = 6.8, 3H), 1.27 (d, *J* = 6.6, 6H); **^{13}C NMR** (125 MHz, MeOD) δ 168.5, 155.9, 141.7, 133.7, 118.0, 109.1, 108.8, 53.6, 47.8, 21.0, 20.9, 20.4, 20.4; **LCMS** (ESI) *m/z* calc'd for $C_{13}H_{18}Br_2NO_2$ $[M+H]^+$ 377.9704, found 377.9719.

Note: Upon synthesis of **31a-(Me)** (Step 1), it was noted that this species exists as a mixture of enantiomers (See HPLC traces Section XI). Based on this observation, the regioisomeric assignment was made given this species is the only di-bromide that could exhibit atropisomers at room temperature. **HPLC** (enantioenriched material obtained from recrystallization, see Section V) 98:2 er (Chiralpak AD-H, 1.0 mL/min, 95:5 hexanes:ethanol): $R_{T(Minor)}$ = 7.4 min, $R_{T(Major)}$ = 8.0 min.

Note: This was the only di-bromide synthesized independently. The other assignments are based on inference (See below).

b. LC/MS and NMR Data Analysis.

Figure S1. LC/MS Data (TIC Trace) of Catalyzed and Uncatalyzed Crude Reaction Mixtures Quenched at Various Time Points.

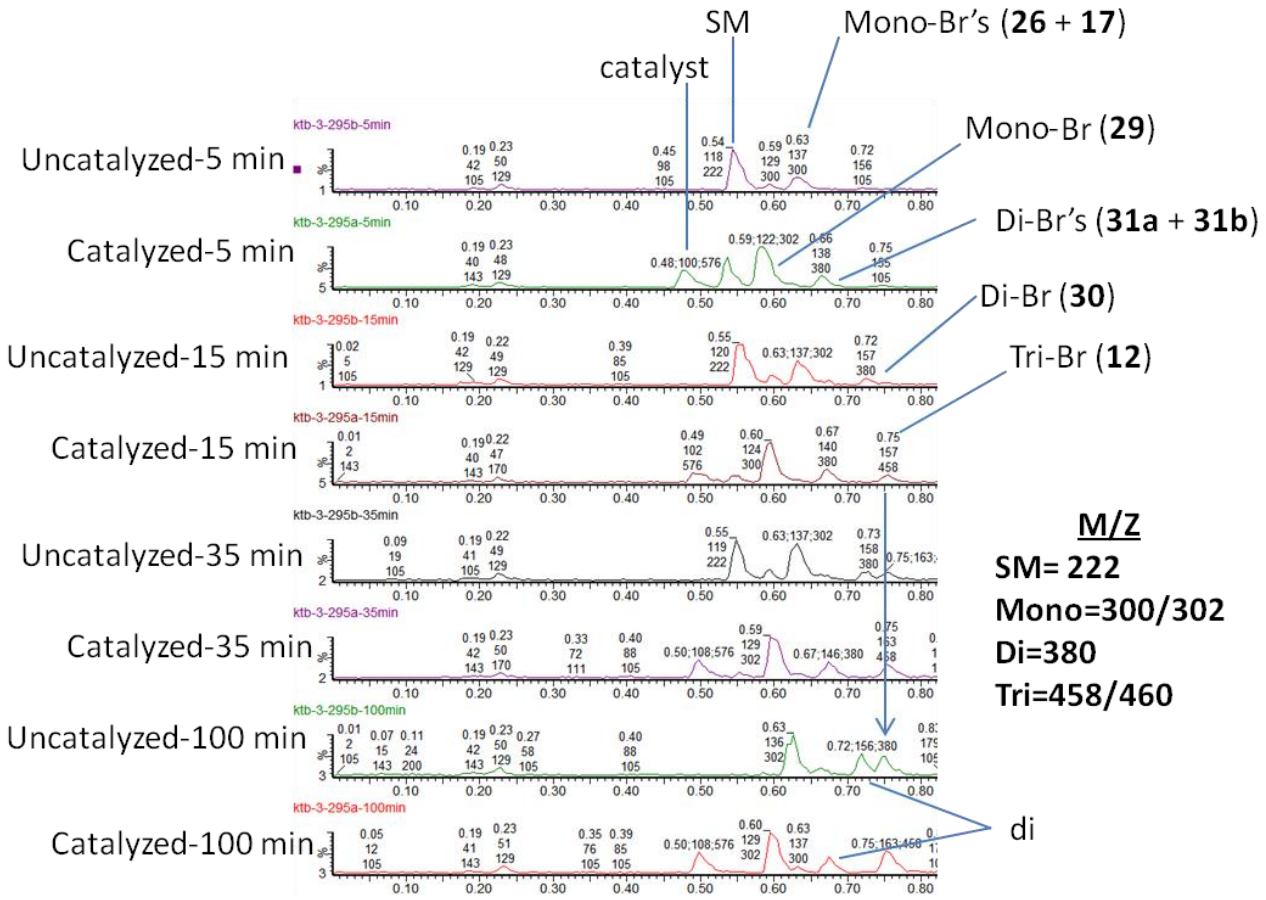


Figure S2: ^{1}H NMR Overlay of Aromatic Region of a) Uncatalyzed and b) Catalyzed Reaction Mixtures at 30 min (500 MHz, DMSO).

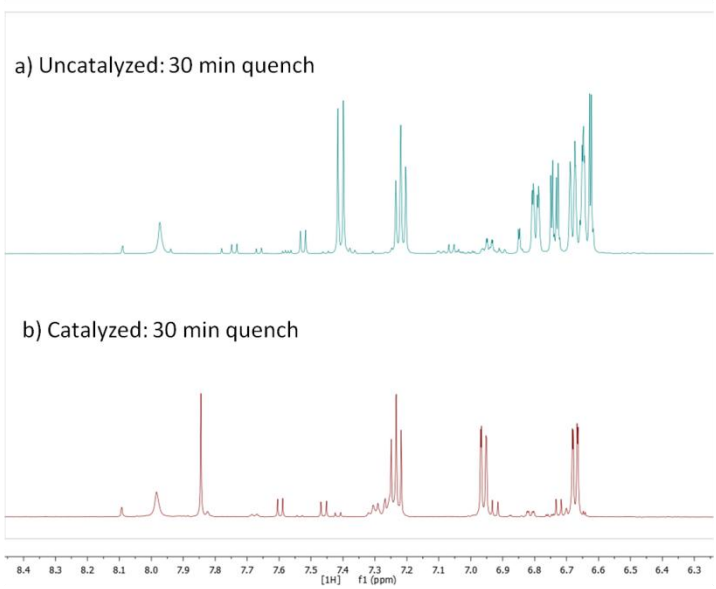


Figure S3. ^{1}H NMR Identification of Major Species in a) Catalyzed and b) Uncatalyzed Reactions at 30 min (500 MHz, DMSO).

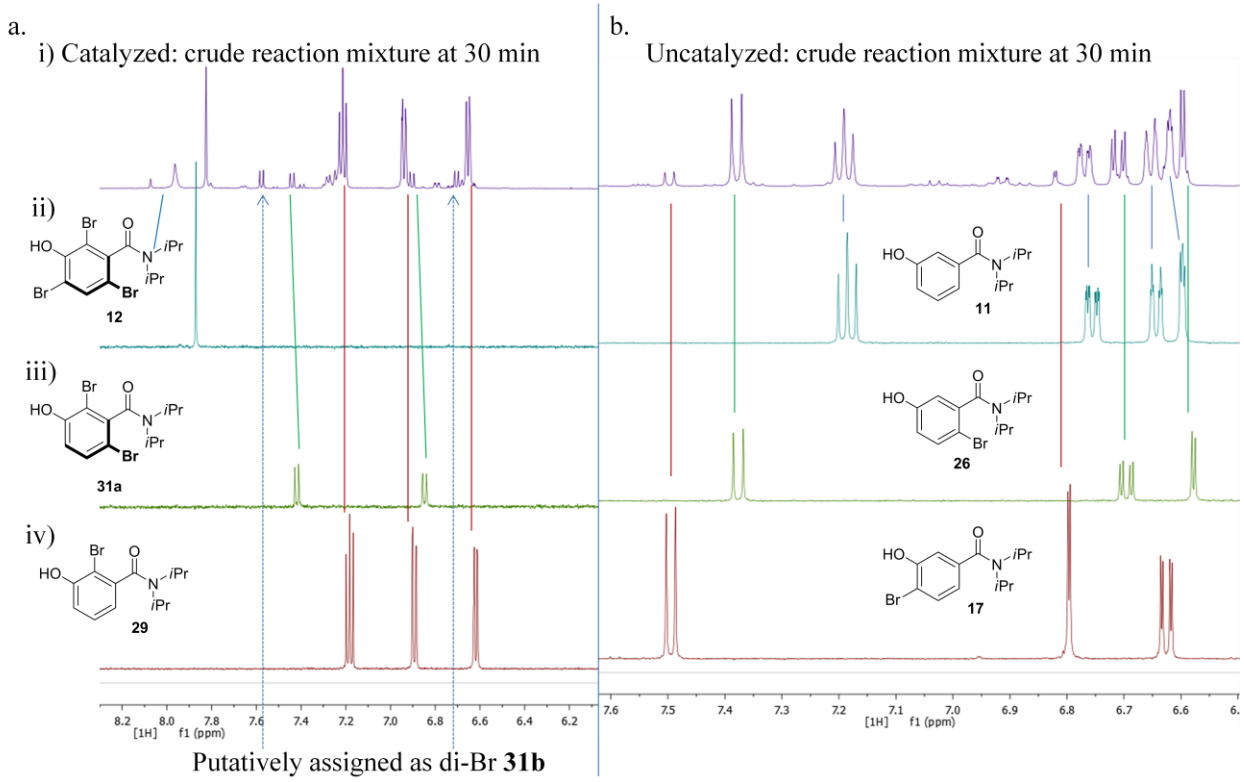
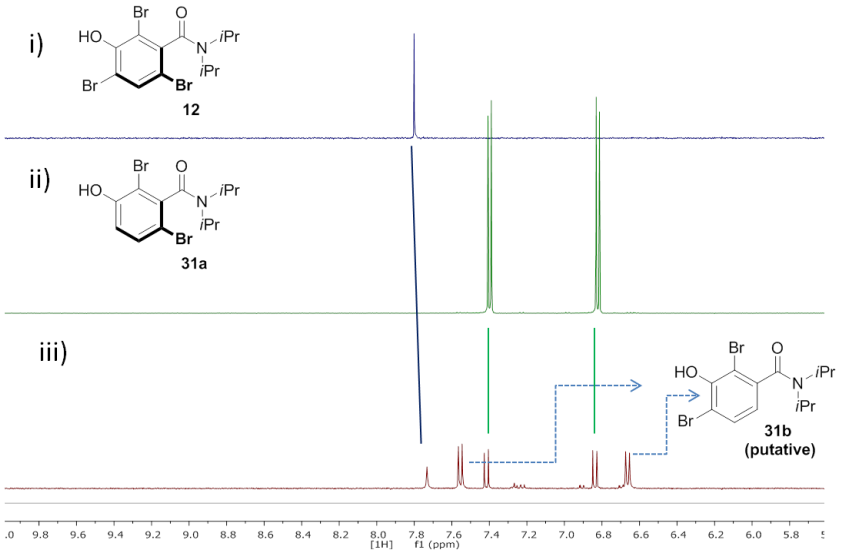


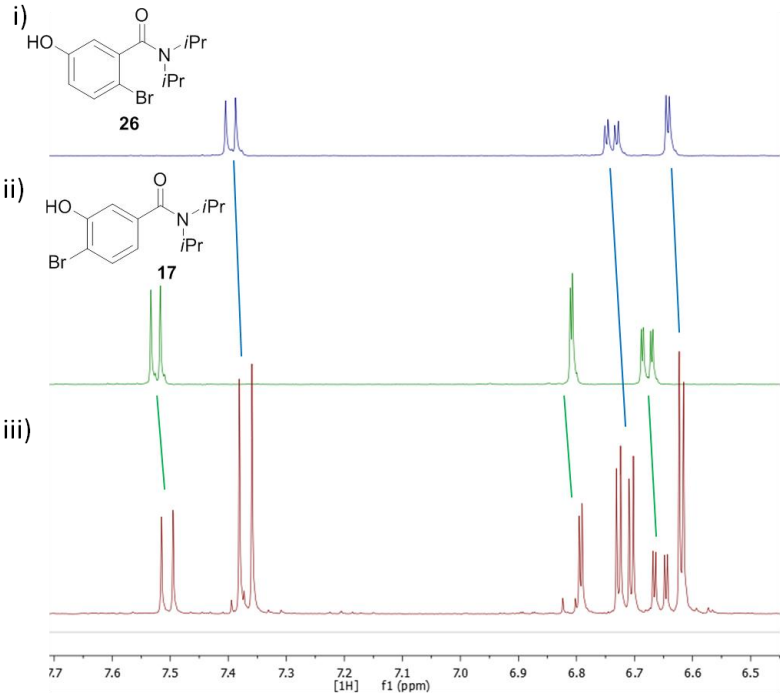
Figure S4. NMR Data Indicating a) Two di-Bromides Present in Purified Fractions of Catalytic Reaction and b) Two Mono-Bromide Species in Uncatalyzed Reaction (500 MHz, MeOD).

a.



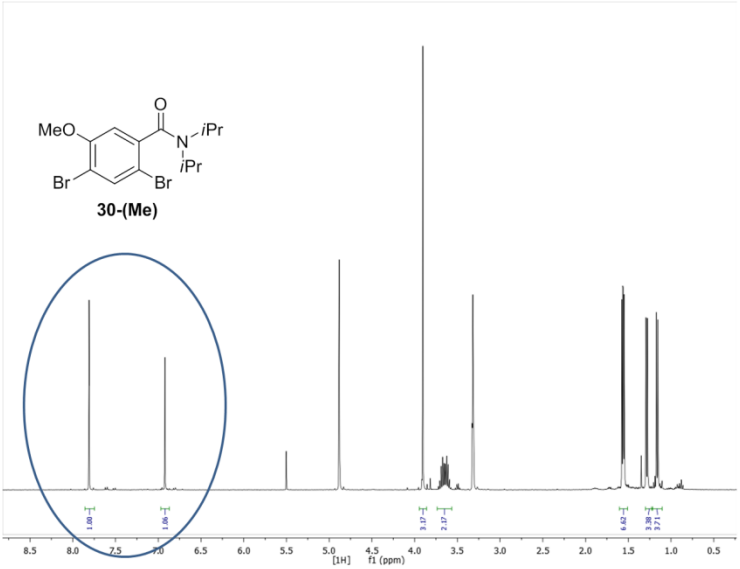
iii) NMR of a mixture isolated from catalytic run, quenched at 1 h, fractions indicating di-Br by LC/MS (m/z=380) show two distinct di-Br present. Dashed arrows = putative species by process of elimination and doublet pattern.

b.



iii) NMR of a mixture isolated from uncatalyzed run, quenched at 1 h, fractions indicating mono-Br by LC/MS (m/z=300) show two distinct mono-Br present.

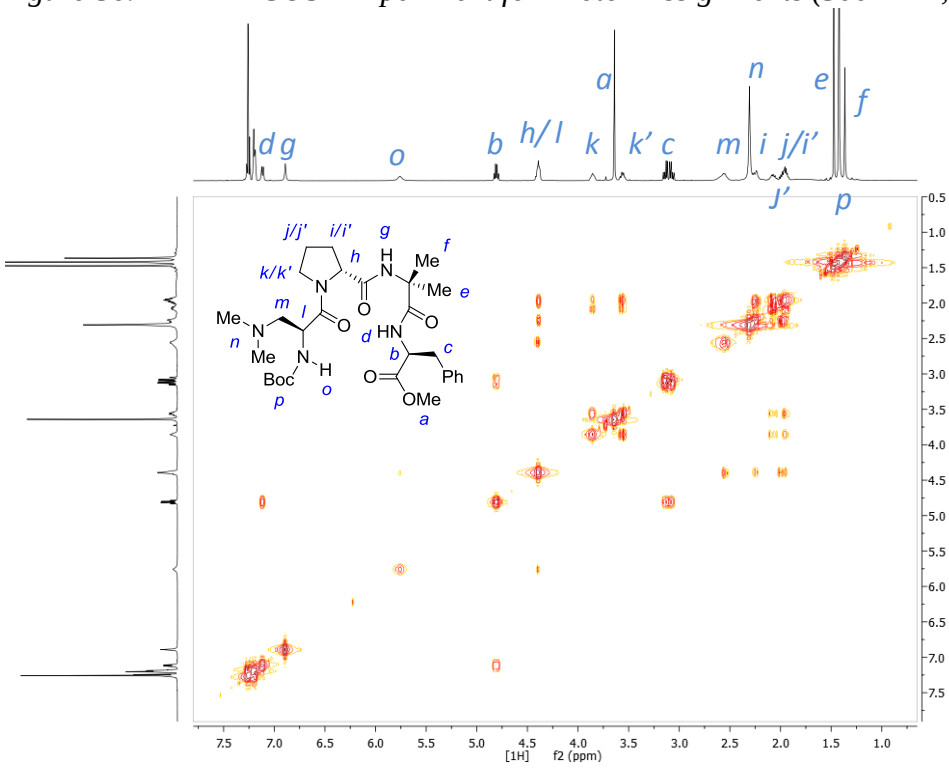
Figure S5. NMR Evidence for Putative di-Br Isolated from From Purification of Uncatalyzed Reaction at 1 h (Methylation Followed for Purification).



Note: Two Singlets in aromatic region that correspond to a Br-substitution pattern of this type (m/z=394).

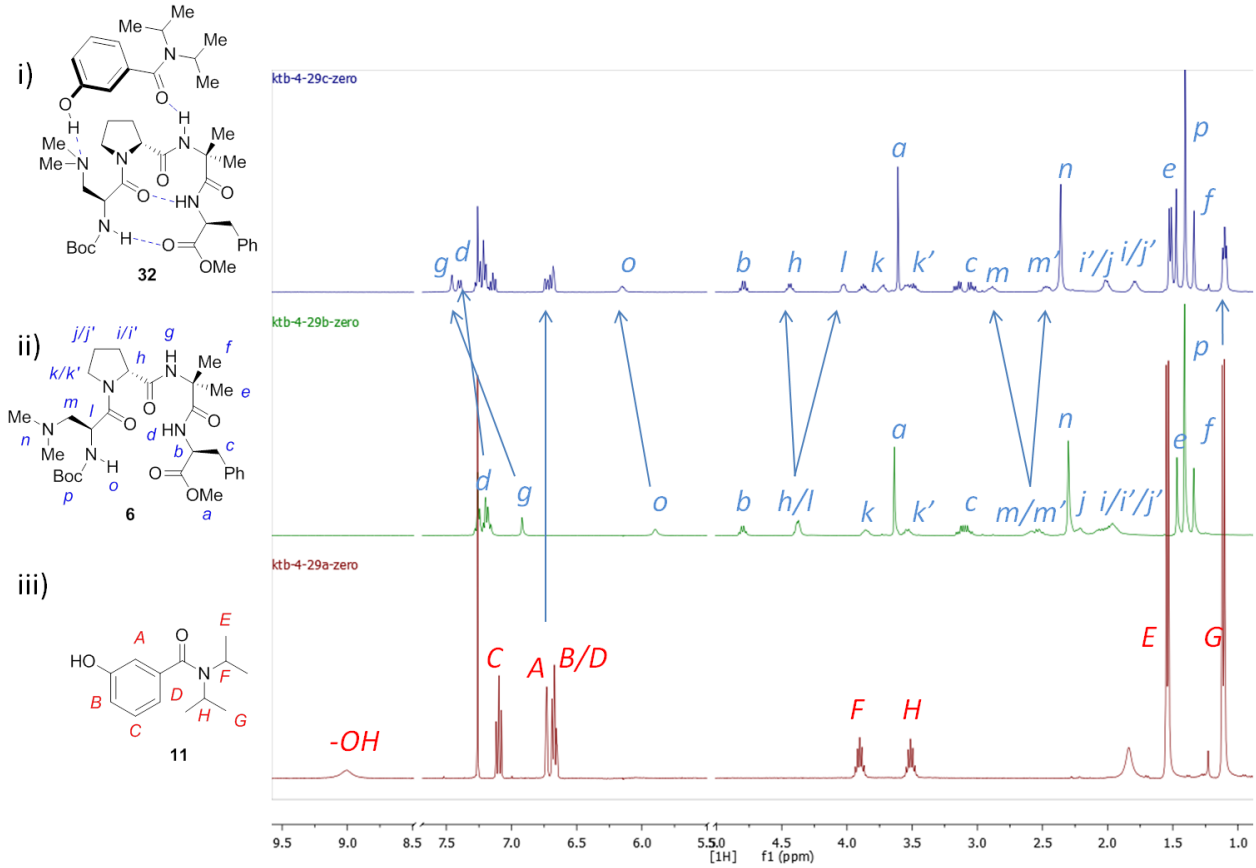
VII. ^{1}H NMR Studies for Catalyst-Substrate Complex.

Figure S6. ^{1}H NMR COSY Experiment for Proton Assignments (500 MHz, $CDCl_3$, 298K).

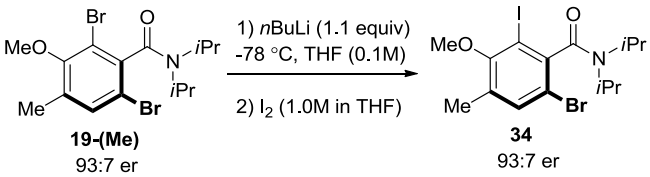


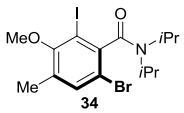
H	assignment	ppm, splitting
C-term OMe	a	2.30, s
α-Phe	b	4.80, dd
β-Phe	c	4.42-4.33, m
NH-Phe	d	7.12, d
Aib-Me	e, f	1.47, 1.36, s,s
NH-Aib	g	6.90, s
α-Pro	h	3.88-3.82, m
β-Pro	i, i'	2.27-2.18, m; 2.02-1.84, m
γ-Pro	j, j'	2.12-2.01, m; 12.02-1.84, m
δ-Pro	k, k'	3.88-3.82, m; 3.59-3.52, m
α-DMAA	l	3.88-3.82, m
β-DMAA	m	2.73-2.43, m
DMAA-Me	n	2.30, s
NH-DMAA	o	5.76, bs
N-term Boc	p	1.42, s

Figure S7. ^{1}*H NMR Data for Complexation (1:1) of Peptide* ***6*** *and Substrate* ***11*** *(*$CDCl_3$*, 0.02M, 400 MHz, 273K).*



VIII. General Method For Selective Lithiation and Iodine Quench.



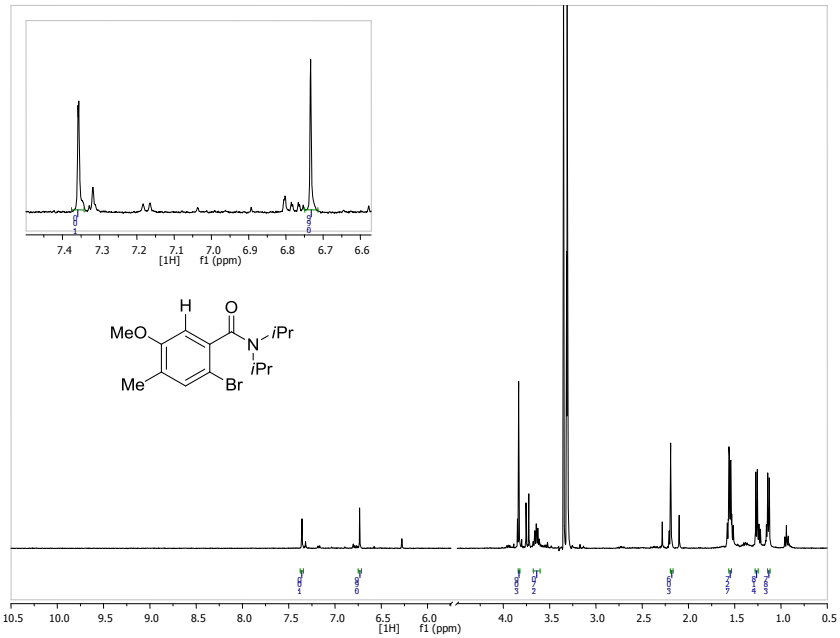


6-bromo-2-iodo-*N*,*N*-diisopropyl-3-methoxy-4-methylbenzamide (34). Step 1: To a flame dried flask, substrate (413.3 mg, 1.02 mmol) was added and dissolved in dry THF (10.1 mL, 0.1 M). The flask was then cooled to -78 ºC and *n*BuLi (465 µL, 1.12 mmol) was added dropwise over the course of five minutes. Step 2: A 1M solution of I_2 in THF (761 mg, 3.00 mmol) was prepared in another flame dried flask and syringed quickly to the reaction flask. The reaction was allowed to stir for ten minutes at -78 ºC and then warmed to room temperature, diluted with ethyl acetate, and washed with sat. $Na_2S_2O_3$. The organic layer was dried and concentrated. The crude residue was purified by silica gel chromatography in 20% ethyl acetate/hexane to afford 313 mg of a pale yellow solid (69% yield). **HPLC** 93:7 er (Chiralpak

AD-H, 1.0 mL/min, 95:5 hexanes:ethanol): $R_{T(Minor)}$ = 5.5 min, $R_{T(Major)}$ = 7.8 min; $[\alpha]_D^{20.0}$ -3.5 (*c* 1.0, $CHCl_3$); **TLC** R_f 0.45 (20% hexanes/ethyl acetate); **IR** (FT-ATR, cm^{-1}) 2966, 1631, 1440, 1353, 1323, 1017; **^{1}H NMR** (500 MHz, MeOD) δ 7.50 (s, 1H), 3.77 (s, 3H), 3.66 (dq, *J* = 13.7, 6.8 Hz, 1H), 3.57 (dq, *J* = 13.3, 6.7 Hz, 1H), 2.35 (s, 3H), 1.61 (d, *J* = 6.8 Hz, 3H), 1.57 (d, *J* = 6.8 Hz, 3H), 1.32 (d, *J* = 6.6 Hz, 3H), 1.27 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR** (125 MHz, MeOD) δ 170.0, 150.7, 143.7, 136.6, 135.0, 114.2, 92.8, 60.8, 53.7, 47.9, 21.2, 21.0, 20.4, 20.3, 16.8; **LCMS** (ESI) *m/z* calc'd for $C_{15}H_{22}BrINO_2$ $[M+H]^+$ 453.9879, found 453.9899.

Note: Regioisomer assigned by quenching lithiated species with H_2O (See Figure S8).

*Figure S8. Crude ^{1}H NMR of Protic Quench of Lithiate Generated From **19-(Me)**. (Inset: Enlargement of aromatic region indicating regioisomer as shown with two distinct singlets, in MeOD).*



IX. References.

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