Supplementary Information

Catalytic, Enantioselective Synthesis of Stilbene cis-Diamines: A Concise Preparation of (-)-Nutlin 3, a Potent p53-MDM2 Inhibitor

Tyler A. Davis and Jeffrey N. Johnston*

Department of Chemistry & Vanderbilt Institute of Chemical Biology
Vanderbilt University
2301 Vanderbilt Place, Nashville, TN 37235-1822

Hoffmann-La Roche Patent Synthesis
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Experimental Section

All reagents and solvents were commercial grade and purified prior to use when necessary. The following reagents were used as supplied by Sigma-Aldrich without further purification except when noted otherwise. Aldimines were prepared as reported in the literature. 1 2,4-Dichloro-6,7-dimethoxyquinoline was prepared with a procedure similar to that of S5 and S7. Toluene was dried by passage through a column of activated alumina as described by Grubbs. 2 Thin layer chromatography (TLC) was performed using glass-backed silica gel (250 μm) plates and flash chromatography utilized 230–400 mesh silica gel from Sorbent Technologies. UV light, and/or the use of potassium iodoplatinate and potassium permanganate solutions were used to visualize products. IRA-900-NO2 resin was prepared by washing IRA900-Cl resin with aq NaNO2 until the wash no longer tested positive for chloride by a AgNO3 test.

Nuclear magnetic resonance spectra (NMR) were acquired on a Bruker DRX-500 (500 MHz), Bruker AV-400 (400 MHz) or Bruker AV II-600 (600 MHz) instrument. Chemical shifts are measured relative to residual solvent peaks as an internal standard set to δ 7.26 and δ 77.0 (CDCl3). IR spectra were recorded on a Thermo Nicolet IR100 spectrophotometer and are reported in wavenumbers (cm⁻¹). Compounds were analyzed as neat films on a NaCl plate (transmission). Mass spectra were recorded on a Waters LCT spectrometer by use of the ionization method noted.

Absolute and relative configuration of 1a was assigned by analogy to S1, for which a crystal structure was obtained (see SI-2).

tert-Butyl (1R,2S)-1-(3-bromo-4-methoxyphenyl)-2-nitro-2-phenylethylcarbamate (S1). tert-Butyl 3-bromo-4-methoxybenzylidenecarbamate (62.8 mg, 200 μmol) and H₄PyrrolidineQuin-BAM (5.1 mg, 10 μmol) were dissolved in toluene (2 mL) at room temperature. The solution was chilled to -78 °C before addition of nitromethylbenzene (41.1 mg, 300 μmol). The reaction was then stirred at -78 °C for 20 h. The reaction was kept at the reaction temperature until filtering through a pad of silica with CH₂Cl₂ and EtOAc. The filtrate was concentrated and then purified by column chromatography (5-40% ethyl acetate in hexanes) to afford a white solid (67.1 mg, 74%) that was found to be 73% ee by chiral HPLC; (Chiralcel IA, 5% iPrOH/hexanes, 1 mL/min, t_r(anti, major) = 61.8 min, t_r(anti, minor) = 29.2 min, t_r(syn, major) = 26.8 min, t_r(syn, minor) = 49.6 min); Mp 157.0-159.0 °C; R_f = 0.19 (20% EtOAc/hexanes); IR (film) 3387, 2979, 1685, 1553 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.55 (dd, J = 7.2, 2.0 Hz, 2H), 7.53 (d, J = 2.0 Hz, 1H), 7.46-7.38 (m, 3H), 7.30-7.25 (dd, J = 8.4, 2.0 Hz, 1H), 6.86 (d, J = 8.4 Hz, 1H), 5.72 (d, J = 10.0 Hz, 1H), 5.58 (dd, J = 9.2, 9.2 Hz, 1H), 4.77 (d, J = 8.8 Hz, 1H), 3.89 (s, 3H), 1.26 (s, 9H); ¹³C NMR (150 MHz, CDCl₃) ppm 156.1, 154.1, 131.9, 131.3, 131.1, 130.3, 128.9 (2C), 128.7 (2C), 127.7, 112.1, 112.0, 94.1, 80.5, 56.2, 55.8, 28.0; HRMS (ESI): Exact mass calcd for C₂₀H₂₃BrN₂NaO₅ [M+Na]⁺ 473.0688, found 473.0711.

Isopropyl 2-isopropoxy-4-methoxybenzoate (S2). Isopropyl bromide (2.926 g, 23.79 mmol) was added to a stirred mixture of 4-methoxysalicylic acid (1.000 g, 5.947 mmol), K₂CO₃ (3.286 g, 23.79 mmol), and dry DMF (30 mL) at room temperature. The mixture was allowed to stir for 20 min before heating to reflux for 31 h. The reaction mixture was cooled to room temperature, treated with KI (98.7 mg, 595 μmol) and stirred for 17 h. The reaction was quenched with 1 M aq HCl then extracted with diethyl ether. The combined organic layers were washed with 1 M aq Na₂CO₃, water, then brine before drying over MgSO₄. Concentration of the dried organic layers resulted in a bronze oil (1.0549 g, 70%) that was pure by ¹H NMR. R_f = 0.16 (5% EtOAc/hexanes); IR (film) 2979, 2936, 1721, 1694, 1608, 1575 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.77 (d, J = 7.2 Hz, 1H), 6.49-6.43 (m, 2H), 5.20 (heptet, J = 6.4 Hz, 1H), 4.55 (heptet, J = 6.0 Hz, 1H), 3.81 (s, 3H), 1.36 (d, J = 6.0 Hz, 6H), 1.33 (d, J = 6.0 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) ppm 165.8, 163.5, 159.3, 133.4, 114.9, 104.9, 101.8, 71.5, 67.5, 55.4, 22.0 (2C); HRMS (Cl): Exact mass calcd for C₁₄H₂₁O₄ [M+H]⁺ 253.1434, found 253.1431.

tert-Butyl (1R,2S)-2-amino-1,2-bis(4-chlorophenyl)ethylcarbamate (S3). The nitroalkane (411.3 mg, 1.000 mmol) was dissolved in MeOH (4.0 mL) at room temperature. CoCl₂ (129.8 mg, 1.000 mmol) was added and the reaction mixture was chilled to 0 °C before NaBH₄ (567.6 mg, 15.00 mmol) was added in three portions over 40 min. The reaction mixture was stirred at 0 °C for an additional 30 min before the mixture was quenched with sat. aq. NH₄Cl. The reaction mixture was adjusted to pH 10 with conc. aq. NH₄OH. The mixture was extracted with ethyl acetate, dried over MgSO₄, and concentrated. Column chromatography (25-45% ethyl acetate in hexanes) of the residue afforded the product as a white solid (251.7 mg, 66%). Mp 149.0-150.0 °C;

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$\alpha^2$ D +67 ($c$ 0.12, CHCl$_3$); R$_f$ = 0.12 (50% EtOAc/hexanes); IR (film) 3377, 2981, 1683, 1523 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.24 (d, $J$ = 8.4 Hz, 2H), 7.21 (d, $J$ = 8.4 Hz, 2H), 7.00 (d, $J$ = 8.4 Hz, 2H), 6.93 (d, $J$ = 8.4 Hz, 2H), 5.49 (d, $J$ = 7.6 Hz, 1H), 4.79 (br s, 1H), 4.23 (br s, 1H), 1.50 (s, 2H), 1.36 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) ppm 155.0, 140.3 (2C), 133.3, 133.2, 128.7, 128.4, 128.2 (2C), 79.8, 59.5, 59.1, 28.2; HRMS: Exact mass calcd for C$_{19}$H$_{23}$Cl$_2$N$_2$O$_2$ [M+H]$^+$ 381.1137, found 381.1147.

N-((1S,2R)-2-Amino-1,2-bis(4-chlorophenyl)ethyl)-2-isopropoxy-4-methoxybenzamide (S4). Amide (180.0 mg, 313.9 $\mu$mol) was dissolved in CH$_2$Cl$_2$ (3.1 mL). TFA (932 $\mu$L, 12.6 mmol) was added and the mixture was stirred at room temperature for 16 h. The reaction mixture was poured into satd. aq. NaHCO$_3$ and extracted with CH$_2$Cl$_2$. The combined organic layers were dried over MgSO$_4$, filtered, and concentrated to a light brown foam (130.3 mg, 88%). $[\alpha]^2_D$ -140 ($c$ 0.11, CHCl$_3$); R$_f$ = 0.46 (10% MeOH/CH$_2$Cl$_2$); IR (film) 3376, 2925, 2853, 1644, 1605, 1521 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.88 (d, $J$ = 8.0 Hz, 1H), 8.13 (d, $J$ = 8.8 Hz, 2H), 7.24 (d, $J$ = 8.4 Hz, 2H), 7.20 (d, $J$ = 8.4 Hz, 2H), 7.03 (d, $J$ = 8.4 Hz, 2H), 7.00 (d, $J$ = 8.8 Hz, 2H), 6.56 (dd, $J$ = 8.8, 2.4 Hz, 1H), 6.49 (d, $J$ = 2.0 Hz, 1H), 5.43 (dd, $J$ = 8.0, 4.8 Hz, 1H), 4.75 (qq, $J$ = 6.0, 6.0 Hz, 1H), 4.41 (d, $J$ = 4.8 Hz, 1H), 3.83 (s, 3H), 1.45 (d, $J$ = 5.6 Hz, 3H), 1.44 (d, $J$ = 5.6 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) ppm 164.7, 163.3, 157.2, 140.7, 136.8, 134.1, 133.2, 129.1, 128.4, 128.3, 128.2, 115.0, 105.1, 100.3, 71.5, 59.0, 58.6, 55.5, 22.2, 22.0; HRMS (ESI): Exact mass calcd for C$_{25}$H$_{27}$Cl$_2$N$_2$O$_3$ [M+H]$^+$ 473.1399, found 473.1400.

2,4-Dichloro-6-methoxyquinoline (S5). Phosphorus(V) oxychloride (40 mL, 1.5 M) was added through a condenser into a 3-neck round bottom flask containing malonic acid (6.244 g, 60.00 mmol) and a stir bar at room temperature. While stirring, $p$-anisidine (9.236 g, 75.00 mmol) was added in small portions over a period of 15 minutes through an open neck of the round bottom flask. The reaction mixture was heated and stirred at reflux for 5 hours. The reaction mixture was allowed to cool to room temperature before it was poured over crushed ice (~700 mL). The pH of the resulting aqueous solution was then adjusted to 10 with concentrated ammonium hydroxide (~85 mL). The aqueous suspension was extracted with dichloromethane. The combined organic layers were then dried over MgSO$_4$ before concentration. Purification by column chromatography (0-5% ethyl acetate in hexanes) yielded the title compound as a slightly yellow solid (4.7812 g, 35%). Mp 170.5-171.5 $^\circ$C; R$_f$ = 0.27 (2% EtOAc/hexanes); IR (film) 3084, 3013, 2982, 1623, 1562, 1499 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.90 (d, $J$ = 9.0 Hz, 1H), 7.45 (s, 1H), 7.40 (dd, $J$ = 9.0, 3.0 Hz, 1H), 7.36 (d, $J$ = 3.0 Hz, 1H), 3.96 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) ppm 158.9, 147.0, 144.0, 142.6, 130.4 126.3, 124.1, 122.0, 101.9, 55.7; HRMS (CI): Exact mass calcd for C$_{10}$H$_8$Cl$_2$NO [M+H]$^+$ 227.9977, found 227.9974.
H,^4Cl,^6MeOQuin-BAM (S6). A 2-5 mL μW vial was charged with (R,R)-diaminocyclohexane (125.2 mg, 1.096 mmol), 2,4-dichloro-6-methoxyquinoline (500 mg, 2.190 mmol), Pd(dba)$_2$ (12.6 mg, 22.0 μmol), *rac*-BINAP (13.6 mg, 22.0 μmol), and sodium tert-butoxide (316.2 mg, 3.290 mmol).^4^ Trifluoromethylbenzene (3.8 mL) was added and the resulting suspension was heated at 120 °C and stirred in the microwave for 10 min. The reaction mixture was triturated with CH$_2$Cl$_2$ and filtered. The filtrate was concentrated and purified by column chromatography (10-20% ethyl acetate in hexanes) to provide a yellow solid (420.3 mg, 77%) that was pure by $^1$H NMR; [α]$^2_0$ +610 (c 0.18, CHCl$_3$); $R_f$ = 0.18 (20% EtOAc/hexanes); IR (film) 3218, 2925, 1605, 1495 cm$^{-1}$; $^1$H NMR (600 MHz, CDCl$_3$, 325 K) δ 7.64 (d, $J$ = 9.0 Hz, 2H), 7.30 (d, $J$ = 3.0 Hz, 2H), 7.25 (dd, $J$ = 9.0, 3.0 Hz, 2H), 6.38 (br s, 2H), 5.72 (br s, 2H), 4.05-3.90 (m, 2H), 3.91 (s, 6H), 2.39-2.25 (m, 2H), 1.90-1.80 (m, 2H), 1.55-1.35 (m, 4H); $^{13}$C NMR (150 MHz, CDCl$_3$, 325 K) ppm 155.5, 155.4, 144.0, 141.4, 127.6, 121.9, 121.8, 111.8, 103.7, 56.1, 55.6, 33.0, 24.9; HRMS (ESI): Exact mass calcd for C$_{26}$H$_{27}$Cl$_2$N$_4$O$_2$ [M+H]$^+$ 497.1511, found 497.1500.

2,4-Dichloro-7-methoxyquinoline (S7). Phosphorus(V) oxychloride (20 mL, 1.3 M) was added through a running condenser into a 3-neck round bottom flask equipped with a stir bar containing malonic acid (2.710 g, 26.00 mmol) at room temperature. While stirring, m-anisidine (4.000 g, 32.48 mmol) was added in small portions over a period of 15 minutes through an open neck of the round bottom flask. The reaction mixture was heated and stirred at reflux for 5 hours. The reaction mixture was allowed to cool to room temperature before it was poured over crushed ice (~350 mL). The pH of the resulting aqueous solution was adjusted to 10 with concentrated ammonium hydroxide. The aqueous suspension was extracted with dichloromethane. The combined organic layers were dried over MgSO$_4$ and filtered before concentration to provide a 2.2:1 mixture ($^1$H NMR) of the 7-methoxy and 5-methoxy regioisomers. Purification by column chromatography (0-8% ethyl acetate in hexanes) yielded a white solid (3.181 g, 54%) that was recrystallized from ethyl acetate and hexanes to provide the 7-methoxy isomer. Mp 131.5-132.5 °C; $R_f$ = 0.18 (5% EtOAc/hexanes); IR (film) 3092, 2982, 1623, 1572, 1559 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.01 (d, $J$ = 9.2 Hz, 1H), 7.32 (s, 1H), 7.23 (dd, $J$ = 9.2, 2.4 Hz, 1H), 3.92 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) ppm 162.2, 150.2, 150.0, 143.9, 125.2, 120.7, 120.1, 119.5, 107.1, 55.7; HRMS (ESI): Exact mass calcd for C$_{10}$H$_{8}$Cl$_2$NO [M+H]$^+$ 227.9977, found 227.9973.

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**H,Cl²MeOQuin-BAM (S8).** A 2-5 mL µW vial was charged with (R,R)-diaminocyclohexane (125.2 mg, 1.096 mmol), 2,4-dichloro-7-methoxyquinoline (500 mg, 2.190 mmol), Pd(dba)₂ (12.6 mg, 22.0 µmol), rac-BINAP (13.6 mg, 22.0 µmol), and sodium tert-butoxide (316.2 mg, 3.290 mmol). Trifluoromethylenzene (3.8 mL) was added and the resulting suspension was heated at 100 °C and stirred in the microwave for 10 min. The reaction mixture was diluted with CH₂Cl₂ and filtered through Celite. The filtrate was concentrated and washed with CH₂Cl₂ then hexanes to provide a light brown powder (1.4612 g, 68%) that was sufficiently pure by ¹H NMR; [α]²⁰ +580 (c 0.19, CHCl₃); Rf = 0.25 (50% EtOAc/hexanes); IR (film) 3220, 2933, 1610, 1510 cm⁻¹; ¹H NMR (500 MHz, CDCl₃, 325 K) δ 7.82 (d, J = 9.0 Hz, 2H), 7.08 (s, 2H), 6.91 (dd, J = 9.0, 2.5 Hz, 2H), 6.31 (br s, 2H), 5.64 (br s, 2H), 4.09 (br s, 2H), 3.94 (s, 6H), 2.41-2.32 (m, 2H), 1.90-1.80 (m, 2H), 1.55-1.38 (m, 4H); ¹³C NMR (100 MHz, CDCl₃, 325 K) ppm 162.0, 157.3, 150.5, 142.3, 125.3, 116.3, 114.4, 109.5, 106.0, 56.1, 55.5, 32.9, 24.9; HRMS (ESI): Exact mass calcd for C₂₆H₂₇Cl₂N₄O₂ [M+H]⁺ 497.1501, found 497.1511.

**H,Cl⁶⁷(MeO)₂Quin-BAM (S9).** A 10-20 mL µW vial was charged with (R,R)-diaminocyclohexane (442.4 mg, 3.874 mmol), 2,4-dichloro-6,7-dimethoxyquinoline (2.000 g, 7.749 mmol), Pd(dba)₂ (44.5 mg, 77.48 µmol), rac-BINAP (48.2 mg, 77.48 µmol), and sodium tert-butoxide (1.117 g, 11.62 mmol). Trifluoromethylenzene (13.4 mL) was added and the resulting suspension was heated at 100 °C and stirred in the microwave for 10 min. The reaction mixture was filtered through celite with CH₂Cl₂ and concentrated. The residue was triturated with ethyl acetate and hexanes to provide a light brown powder (412.9 mg, 76%) that was pure by ¹H NMR; [α]²⁰ +410 (c 0.10, CHCl₃); Rf = 0.15 (50% EtOAc/hexanes); IR (film) 3223, 2930, 1600 cm⁻¹; ¹H NMR (500 MHz, CDCl₃, 325 K) δ 7.24 (s, 2H), 7.09 (s, 2H), 6.32 (br s, 2H), 5.50 (br s, 2H), 4.02 (s, 6H), 4.00 (br s, 2H), 3.97 (s, 6H), 2.38-2.28 (m, 2H), 1.90-1.80 (m, 2H), 1.55-1.35 (m, 4H); ¹³C NMR (100 MHz, CDCl₃, 330 K) ppm 156.2, 153.2, 147.1, 145.3, 141.0, 115.7, 109.2, 106.6, 103.6, 56.2 (2C), 56.1, 33.0, 24.9; HRMS (Cl): Exact mass calcd for C₂₈H₂₇Cl₂N₄O₄ [M+H]⁺ 557.1717, found 557.1717.

**N-((1R,2S)-1,2-Bis(4-chlorophenyl)-2-(2-isopropoxy-4-methoxybenzamido)ethyl)-3-oxopiperazine-1-carboxamide (S10).** Amine (100.0 mg, 211.2 µmol) was dissolved in CH₂Cl₂ (1.0 mL) and stirred at room temperature.
temperature. CDI (41.1 mg, 253.5 \mumol) was added and the reaction was stirred for 1 h. 2-Oxo-piperazine (42.3 mg, 422.4 \mumol) was added, and the reaction mixture was stirred for an additional 4 hours. The reaction mixture was concentrated and purified by column chromatography (0-2-5% methanol in dichloromethane) to provide a white solid (119.6 mg, 94%). \([\alpha]_D^{20} +110 \text{ (c 0.14, CHCl}_3); \; R_f = 0.34 \text{ (10\% MeOH/CH}_2\text{Cl}_2); \; \text{IR (film) 3369, 2978, 2932, 2243, 1634, 1605 \text{ cm}^{-1}; \; ^1H \text{ NMR (400 MHz, CDCl}_3) \; \delta 8.37 \text{ (d, } J = 8.0 \text{ Hz, 1H), 8.28 \text{ (d, } J = 8.8 \text{ Hz, 1H), 7.80 \text{ (d, } J = 4.8 \text{ Hz, 1H), 7.29 \text{ (d, } J = 8.4 \text{ Hz, 2H), 7.17 \text{ (d, } J = 8.4 \text{ Hz, 2H), 6.95 \text{ (d, } J = 8.4 \text{ Hz, 2H), 6.88 \text{ (d, } J = 8.4 \text{ Hz, 2H), 6.62 \text{ (dd, } J = 8.20 \text{ Hz, 2H), 6.46 \text{ (d, } J = 2.0 \text{ Hz, 1H), 6.15 \text{ (br s, 1H), 5.77 \text{ (dd, } J = 7.6, 2.0 \text{ Hz, 1H), 5.10 \text{ (dd, } J = 8.8, 2.4 \text{ Hz, 1H), 4.66 \text{ (qq, } J = 6.0, 6.0 \text{ Hz, 1H), 4.15 \text{ (d, } J = 2.4 \text{ Hz, 2H), 3.86 \text{ (s, 3H), 3.73 \text{ (dd, } J = 13.2, 5.6, 4.4 \text{ Hz, 1H), 3.60 \text{ (ddd, } J = 13.2, 6.4, 4.4 \text{ Hz, 1H), 3.46-3.35 \text{ (m, 2H), 1.20 \text{ (d, } J = 6.0 \text{ Hz, 3H), 1.14 \text{ (d, } J = 6.0 \text{ Hz, 3H); } \; ^13C \text{ NMR (100 MHz, CDCl}_3) \; \text{ppm 168.0, 167.0, 163.0, 157.2, 155.9, 136.7, 136.6, 134.3, 133.8, 133.2, 129.4, 128.6, 128.4, 128.0, 113.5, 105.4, 100.3, 71.4, 61.6, 57.5, 55.5, 47.4, 40.9, 39.9, 21.9, 21.5; \; \text{HRMS (CI): Exact mass calced for } C_{39}H_{33}Cl_2N_2O_4 [M+H]^+ 599.1823, \text{ found 599.1814.}})

**Supporting Information**

**tert-Butyl (1R,2S)-1,2-bis-(4-chlorophenyl)-2-nitroethylcarbamate (1a).** Imine (1.5000 g, 6.2580 mmol) and H\(^4\)Pyrrolidine\(^6,7\)(MeO\(_2\)Quin-BAM (196.1 mg, 312.9 \mumol) were dispersed into a 100 mL round bottom flask equipped with stir bar. Toluene (63 mL) was added and the mixture was chilled to -78 °C before addition of the nitroalkane 9 (1.1810 g, 6.8840 mmol). The reaction was stirred at -78 °C for 24 h. The reaction was kept at the reaction temperature and filtered directly through a pad of silica gel with CH\(_2\)Cl\(_2\). The filtrate was concentrated and purified by column chromatography (0-2-5% methanol in dichloromethane) to provide a colorless crystalline material (586.8 mg) was separated from the mother liquor and found to be >200:1 dr, 97% ee by chiral HPLC; (Chiralcel AD-H, 12% \text{PrOH/hexanes, 1 mL/min, } t_r(anti, major) = 30.5 \text{ min, } t_r(anti, minor) = 12.8 \text{ min, } t_r(syn, major) = 14.9 \text{ min, } t_r(syn, minor) = 45.6 \text{ min). Mp 172.0-174.0 °C; [\alpha]_D^{20} -150 \text{ (c 0.13, CHCl}_3); \; R_f = 0.24 \text{ (20\% EtOAc/hexanes); IR (film) 3369, 2982, 1682, 1551, 1521 \text{ cm}^{-1}; \; ^1H \text{ NMR (400 MHz, CDCl}_3) \; \delta 7.50 \text{ (d, } J = 9.6 \text{ Hz, 1H), 5.58 \text{ (dd, } J = 9.6, 9.6 \text{ Hz, 1H), 4.78 \text{ (d, } J = 9.6 \text{ Hz, 1H), 1.28 \text{ (s, 9H); } \; ^13C \text{ NMR (150 MHz, CDCl}_3) \; \text{ppm 154.2, 136.6, 135.6, 134.9, 130.1, 129.7, 129.3, 129.1, 128.6, 93.2, 80.8, 56.1, 28.0; \; \text{HRMS (CI): Exact mass calced for } C_{39}H_{28}Cl_2N_2O_4 [M+H]^+ 411.0873, \text{ found 411.0865.}})

**General Procedure for the Synthesis of Adducts 1b-m.** Imine (100 \mumol) and 6,7(MeO\(_2\)PBAM (8d) (3.1 mg, 5.0 \mumol) were dispersed into a vial with a stir bar. Toluene (1.0 mL) was added, and the reaction was stirred at room temperature until homogenous. The reaction mixture was chilled to -78 °C before nitroalkane (110 \mumol) was added. The reaction mixture was stirred for 18-26 h. The chilled mixture was diluted with CH\(_2\)Cl\(_2\) and quickly filtered through a pad of silica. The silica pad was flushed with EtOAc. The filtrate was concentrated and purified by column chromatography.

**tert-Butyl (1R,2S)-1-(4-chlorophenyl)-2-nitro-2-phenylethylcarbamate (1b).** Column chromatography (7-20% ethyl acetate in hexanes) afforded a white solid (35.0 mg, 93%) that was found to be 90% ee and 19:1 dr.
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by chiral HPLC; (Chiralcel IA, 5% i-PrOH/hexanes, 1 mL/min, 230 nm, \(t(anti, \text{ major}) = 20.4\) min, \(t(anti, \text{ minor}) = 27.7\) min, \(t(syn, \text{ major}) = 24.3\) min, \(t(syn, \text{ minor}) = 46.1\) min); mp 177.5-178.5 °C; \([\alpha]_D^{20} -28.2\) (c 0.11, CHCl₃); \(R_f = 0.29\) (20% EtOAc/hexanes); IR (film) 3386, 2984, 2924, 1683, 1549, 1520 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 7.54 (d, \(J = 6.6\) Hz, 2H), 7.42 (m, 1H), 7.42 (d, \(J = 6.6\) Hz, 2H), 7.34 (d, \(J = 9.0\) Hz, 2H), 7.29 (d, \(J = 8.4\) Hz, 2H), 5.76 (br s, 1H), 5.62 (br s, 1H), 4.84 (br s, 1H), 1.26 (s, 9H); ¹³C NMR (150 MHz, CDCl₃) ppm 154.2, 130.4, 129.2, 128.9, 128.6, 80.6, 56.1, 28.2. HRMS (ESI): Exact mass calcd for C₁₉H₂₁ClN₂NaO₄ \([M+Na]^+\) 399.1088, found 399.1070.

**tert-Butyl (1R,2S)-1-(4-(allyloxy)phenyl)-2-nitro-2-phenylethylcarbamate (1c).** Product was made according to the general procedure with the exception that 120 µmol of imine and 100 µmol of nitroalkane were used. Column chromatography (7-25% ethyl acetate in hexanes) afforded a white solid (28.0 mg, 79%) that was found to be 87% ee and 38:1 dr by chiral HPLC; (Chiralcel IA, 12% i-PrOH/hexanes, 0.5 mL/min, \(t(anti, \text{ major}) = 14.9\) min, \(t(anti, \text{ minor}) = 13.1\) min, \(t(syn, \text{ major}) = 13.8\) min, \(t(syn, \text{ minor}) = 22.3\) min); Mp 174.5-176.0 °C; \([\alpha]_D^{20} -42\) (c 0.16, CHCl₃); \(R_f = 0.21\) (20% EtOAc/hexanes); IR (film) 3394, 2981, 2930, 1683, 1549, 1514 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 7.57 (d, \(J = 7.8\) Hz, 2H), 7.45-7.37 (m, 3H), 7.26 (d, \(J = 8.4\) Hz, 2H), 6.89 (d, \(J = 8.4\) Hz, 2H), 6.04 (dddd, \(J = 16.8, 10.2, 4.8, 4.8\) Hz, 1H), 5.74 (br s, 1H), 5.61 (br s, 1H), 5.41 (ddd, \(J = 17.4, 1.2\) Hz, 1H), 5.29 (dd, \(J = 10.2, 1.2\) Hz, 1H), 4.80 (d, \(J = 7.8\) Hz, 1H), 4.52 (d, \(J = 4.8\) Hz, 2H) 1.25 (s, 9H); ¹³C NMR (150 MHz, CDCl₃) ppm 158.8, 154.2, 133.0, 131.6, 130.1, 129.7, 128.8 (2C), 128.4, 117.8, 115.1, 94.4, 80.3, 68.8, 56.1, 28.0; HRMS (ESI): Exact mass calcd for C₂₂H₂₆N₂NaO₅ \([M+Na]^+\) 421.1739, found 421.1730.

**tert-Butyl (1R,2S)-1-(4-methoxyphenyl)-2-nitro-2-phenylethylcarbamate (1d).** Product was made according to the general procedure with the exception that reaction warmed to -20 °C and stirred for 1h before filtration. Column chromatography (7-20% ethyl acetate in hexanes) afforded a white solid (31.0 mg, 83%) that was found to be 85% ee and 81:1 dr by chiral HPLC; (Chiralcel IA, 12% i-PrOH/hexanes, 0.5 mL/min, \(t(anti, \text{ major}) = 21.3\) min, \(t(anti, \text{ minor}) = 23.6\) min, \(t(syn, \text{ major}) = 19.8\) min, \(t(syn, \text{ minor}) = 37.0\) min); Mp 161.0-162.5 °C; \([\alpha]_D^{20} -43\) (c 0.14, CHCl₃); \(R_f = 0.18\) (20% EtOAc/hexanes); IR (film) 3390, 2980, 2930, 1683, 1548, 1515 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.60-7.53 (m, 2H), 7.44-7.37 (m, 3H), 7.27 (d, \(J = 8.8\) Hz, 2H), 6.88 (d, \(J = 8.8\) Hz, 2H), 5.75 (d, \(J = 10.0\) Hz, 1H), 5.61 (dd, \(J = 9.2, 9.2\) Hz, 1H), 4.80 (d, \(J = 8.8\) Hz, 1H), 3.80 (s, 3H), 1.25 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) ppm 159.7, 154.2, 131.6, 130.1, 129.5, 128.8 (2C), 128.4, 114.3, 94.4, 80.3, 56.2, 55.3, 28.0; HRMS (ESI): Exact mass calcd for C₂₀H₂₄N₂NaO₄ \([M+Na]^+\) 395.1583, found 395.1567.

**tert-Butyl (1R,2S)-2-nitro-2-phenyl-1-p-tolylethylcarbamate (1e).** Product was made according to the general procedure with the exception that 120 µmol of imine and 100 µmol of nitroalkane were used. Column chromatography (7-20% ethyl acetate in hexanes) afforded a white solid (33.0 mg, 93%) that was found to be 91% ee and 38:1 dr by chiral HPLC; (Chiralcel IA, 12% i-PrOH/hexanes, 0.7 mL/min, \(t(anti, \text{ major}) = 12.1\) min, \(t(anti, \text{ minor}) = 13.1\) min, \(t(syn, \text{ major}) = 11.2\) min, \(t(syn, \text{ minor}) = 20.7\) min); Mp 181.0-183.0 °C; \([\alpha]_D^{20} -46
tert-Butyl (1R,2S)-1-(4-fluorophenyl)-2-nitro-2-phenylethylcarbamate (1f). Product was made according to the general procedure with the exception that 120 μmol of imine and 100 μmol of nitroalkane were used. Column chromatography (7-25% ethyl acetate in hexanes) afforded a white solid (35.0 mg, 97%) that was found to be 87% ee and 15:1 dr by chiral HPLC; (Chiralcel IA, 5% EtOH/hexanes, 0.5 mL/min, \( t(anti) \), major) 19.1 min, \( t(syn) \), minor) = 20.5 min, \( t(syn) \), major) = 22.8 min, \( t(syn) \), minor) = 39.9 min;Mp 178.5-180.0 °C; [\( \alpha \)]\(_D\)\(^{20} = -18\) (c 0.15, CHCl\(_3\)); \( R_f = 0.34\) (20% EtOAc/hexanes); IR (film) 3391, 2986, 2925, 1683 cm\(^{-1}\); \( ^1\)H NMR (600 MHz, CDCl\(_3\)) \( \delta \) 7.58 (dd, \( J = 7.2, 1.2 \) Hz, 3H), 7.46-7.39 (m, 3H), 7.34 (dd, \( J = 8.4, 4.8 \) Hz, 2H), 7.05 (dd, \( J = 8.4, 8.4 \) Hz, 2H), 5.75 (br s, 1H), 5.64 (br s, 1H), 4.81 (d, \( J = 9.0 \) Hz, 1H), 1.26 (s, 9H); \( ^{13}\)C NMR (150 MHz, CDCl\(_3\)) ppm 162.7 (6J\(_{CF} = 246 \) Hz), 154.2, 133.4, 131.3, 130.3, 129.0 (6J\(_{CF} = 9.0 \) Hz), 128.9, 128.7, 116.0 (6J\(_{CF} = 23 \) Hz), 94.2, 80.6, 56.2, 28.0; \(^{19}\)F NMR (376 MHz, CDCl\(_3\)) ppm -112.7; HRMS (ESI): Exact mass calcd for C\(_{19}\)H\(_{21}\)FN\(_2\)NaO\(_4\) [M+Na\(^+\)] 383.1383, found 383.1392.

tert-Butyl (1R,2S)-2-nitro-2-phenyl-1-(4-(trifluoromethyl)phenyl)ethylcarbamate (1g). Product was made according to the general procedure with the exception that 120 μmol of imine and 100 μmol of nitroalkane were used. Column chromatography (7-20% ethyl acetate in hexanes) afforded a white solid (40.8 mg, 99%) that was found to be 84% ee and 14:1 dr by chiral HPLC; (Chiralcel IA, 8% \(^1\)PrOH/hexanes, 1 mL/min, \( t(anti) \), major) 9.2 min, \( t(syn) \), major) = 13.9 min, \( t(syn) \), major) = 12.6 min, \( t(syn) \), minor) = 20.0 min;Mp 193.5-194.5 °C; [\( \alpha \)]\(_D\)\(^{20} = -21\) (c 0.14, CHCl\(_3\)); \( R_f = 0.33\) (20% EtOAc/hexanes); IR (film) 3390, 2985, 1683, 1548, 1521 cm\(^{-1}\); \( ^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.63 (d, \( J = 8.0 \) Hz, 2H), 7.58-7.53 (m, 2H), 7.49 (d, \( J = 8.4 \) Hz, 2H), 7.43-7.40 (m, 3H), 5.80 (br s, 1H), 5.71 (br s, 1H), 4.89 (br s, 1H), 1.26 (s, 9H); \( ^{13}\)C NMR (100 MHz, CDCl\(_3\)) ppm 141.5, 131.0, 130.9 (6J\(_{CF} = 32 \) Hz), 130.5, 129.0, 128.6, 127.7, 126.0 (6J\(_{CF} = 4.0 \) Hz), 123.8 (6J\(_{CF} = 271 \) Hz), 93.7, 80.8, 56.3, 28.0; \(^{19}\)F NMR (282 MHz, CDCl\(_3\)) ppm -61.1; HRMS (ESI): Exact mass calcd for C\(_{20}\)H\(_{21}\)F\(_3\)N\(_2\)NaO\(_4\) [M+Na\(^+\)] 433.1351, found 433.1364.

tert-Butyl (1R,2S)-1-(biphenyl-4-yl)-2-nitro-2-phenylethylcarbamate (1h). Product was made according to the general procedure with the exception that 120 μmol of imine and 100 μmol of nitroalkane were used. Column chromatography (7-20% ethyl acetate in hexanes) afforded a white solid (41.5 mg, 99%) that was found to be 93% ee and 44:1 dr by chiral HPLC; (Chiralcel AD-H, 10% \(^1\)PrOH/hexanes, 1 mL/min, \( t(anti) \), major) 32.6 min, \( t(anti) \), minor) = 23.9 min, \( t(syn) \), major) = 26.1 min, \( t(syn) \), minor) = 28.7 min;Mp 194.0-196.0 °C; [\( \alpha \)]\(_D\)\(^{20} = -56\) (c 0.15, CHCl\(_3\)); \( R_f = 0.29\) (20% EtOAc/hexanes); IR (film) 3398, 2978, 2922, 1686, 1548, 1520 cm\(^{-1}\); \( ^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.63-7.55 (m, 6H), 7.47-7.40 (m, 7H), 7.39-7.33 (m, 1H), 5.82 (br s, 3H), 3.65 (br s, 3H), 2.23 (s, 3H), 1.24 (s, 9H); \( ^{13}\)C NMR (100 MHz, CDCl\(_3\)) ppm 148.2, 146.9, 133.0, 131.9, 130.9, 128.6, 127.7, 126.0 (q, 6J\(_{CF} = 13 \) Hz), 123.8 (q, 6J\(_{CF} = 13 \) Hz), 93.7, 80.8, 56.3, 28.0; \(^{19}\)F NMR (282 MHz, CDCl\(_3\)) ppm -57.1; HRMS (ESI): Exact mass calcd for C\(_{25}\)H\(_{24}\)FN\(_2\)NaO\(_4\) [M+Na\(^+\)] 483.1439, found 483.1447.
tert-Butyl \(1R,2S\)-1-(naphthalen-2-yl)-2-nitro-2-phenylethylcarbamate (1i). Product was made according to the general procedure with the exception that 120 \(\mu\)mol of imine and 100 \(\mu\)mol of nitroalkane were used. Column chromatography (7-20% ethyl acetate in hexanes) afforded a white solid (38.9 mg, 99%) that was found to be 91% ee and 25:1 dr by chiral HPLC; (Chiralcel IA, 12% \(i\)PrOH/hexanes, 1 mL/min, \(t_{(anti)},\) major) 10.6 min, \(t_{(anti),\} minor) = 13.2 min, \(t_{(syn), major) = 9.2 min, \(t_{(syn), minor) = 17.5 min\); Mp 183.0-184.5 °C; \(\alpha\) \(\alpha\) \(\alpha\) D -39 (c 0.11, CHCl3); \(R_f\) = 0.29 (20% EtOAc/hexanes); IR (film) 3403, 2977, 1688, 1547, 1519 cm \(-1\); \(1H NMR (400 MHz, CDCl_3) \delta 7.89-7.80 (m, 4H), 7.65-7.58 (m, 2H), 7.54-7.48 (m, 2H), 7.48-7.40 (m, 4H), 5.97-5.80 (m, 2H), 4.90 (d, \(J = 8.4 Hz, \) 1H), 1.25 (s, 9H); 13C NMR (100 MHz, CDCl_3) ppm 154.2, 134.8, 133.23, 133.16, 131.5, 130.2, 129.1, 128.9, 128.8, 128.1, 127.7, 126.7, 126.6 (2C), 124.4, 94.2, 80.3, 56.7, 28.0; HRMS (ESI): Exact mass calcd for C_{23}H_{24}N_{2}NaO_{4} [M+Na]^+ 415.1634, found 415.1635.

tert-Butyl \(1R,2S\)-2-(3-bromophenyl)-1-(4-chlorophenyl)-2-nitroethylcarbamate (1j). Column chromatography (7-25% ethyl acetate in hexanes) afforded a white solid (41.5 mg, 91%) that was found to be 89% ee and 13:1 dr by chiral HPLC; (Chiralcel AD-H, 15% \(i\)PrOH/hexanes, 1 mL/min, \(t_{(anti), major) = 29.7 min, \(t_{(anti), minor) = 14.6 min, \(t_{(syn), major) = 13.4 min, \(t_{(syn), minor) = 17.2 min); Mp 178.0-179.0 °C; \(\alpha\) \(\alpha\) \(\alpha\) D -39 (c 0.15, CHCl3); \(R_f\) = 0.40 (20% EtOAc/hexanes); IR (film) 3388, 2982, 1681, 1549, 1519 cm \(-1\); \(1H NMR (400 MHz, CDCl_3) \delta 7.71 (br s, 1H), 7.58 (ddd, \(J = 8.0, 1.6, 0.8 Hz, \) 1H), 7.52 (br d, \(J = 8.0 Hz, \) 1H), 7.35 (d, \(J = 8.8 Hz, \) 1H), 7.29 (dd, \(J = 7.6, 7.6 Hz, \) 1H), 7.29 (d, \(J = 8.8 Hz, \) 2H), 5.75 (br s, 1H), 5.56 (br m, 1H), 4.87 (br s, 1H), 1.29 (s, 9H); 13C NMR (100MHz, CDCl 3) ppm 154.2, 135.6, 134.9, 133.5, 133.3, 131.8, 130.4, 129.3, 128.6, 127.2, 122.8, 93.1, 80.8, 56.3, 28.0; HRMS (ESI): Exact mass calcd for C_{19}H_{20}BrClN_{2}NaO_{4} [M+Na]^+ 477.0193, found 477.0197.

tert-Butyl \(1R,2S\)-1-(4-chlorophenyl)-2-(naphthalen-2-yl)-2-nitroethylcarbamate (1k). Column chromatography (7-25% ethyl acetate in hexanes) afforded a white solid (42.1 mg, 99%) that was found to be 80% ee and 10:1 dr by chiral HPLC; (Chiralcel AD-H, 15% \(i\)PrOH/hexanes, 1 mL/min, \(t_{(anti), major) = 53.9 min, \(t_{(anti), minor) = 18.0 min, \(t_{(syn), major) = 16.7 min, \(t_{(syn), minor) = 26.3 min); Mp 185.5-187.0 °C; \(\alpha\) \(\alpha\) \(\alpha\) D -27 (c 0.15, CHCl3); \(R_f\) = 0.32 (20% EtOAc/hexanes); IR (film) 3388, 2980, 1683, 1550, 1520 cm \(-1\); \(1H NMR (400 MHz, CDCl_3) \delta 8.01 (br s, 1H), 7.92-7.85 (m, 3H), 7.65 (dd, \(J = 8.8, 2.0 Hz, \) 1H), 7.59-7.52 (m, 2H), 7.38-7.32 (m, 4H), 5.95 (br d, \(J = 8.8 Hz, \) 1H), 5.72 (br dd, \(J = 9.2, 9.2 Hz, \) 1H), 4.86 (d, \(J = 8.8 Hz, \) 1H), 1.18 (s, 9H); 13C NMR (100 MHz, CDCl_3) ppm 154.2, 136.1, 134.7, 134.0, 132.8, 129.3, 129.2, 129.0, 128.7, 128.6, 128.3, 127.7, 127.4, 126.9, 124.6, 94.2, 80.7, 56.0, 28.0; HRMS (ESI): Exact mass calcd for C_{23}H_{23}ClN_{2}NaO_{4} [M+Na]^+ 449.1244, found 449.1256.
**tert-Butyl (1R,2S)-1-(4-chlorophenyl)-2-(4-methoxyphenyl)-2-nitroethylcarbamate (1I).** Product was made according to the general procedure with the exception that reaction warmed to -20 °C and stirred for 1 h before filtration. Column chromatography (7-25% ethyl acetate in hexanes) afforded a white solid (36.5 mg, 90%) that was found to be 86% ee and 17:1 dr by chiral HPLC; (Chiralcel AD-H, 15% iPrOH/hexanes, 1 mL/min, t<sub>(anti, major)</sub> 27.6 min, t<sub>(anti, minor)</sub> = 14.3 min, t<sub>(syn, major)</sub> = 16.7 min, t<sub>(syn, minor)</sub> = 37.9 min; Mp 165.0-166.0 °C; [α]<sub>D</sub> = -9.1 (c 0.11, CHCl<sub>3</sub>); R<sub>f</sub> = 0.27 (20% EtOAc/hexanes); IR (film) 3405, 2981, 2926, 1681, 1551, 1522 cm<sup>-1</sup>; 1H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.47 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H), 6.92 (d, J = 8.4 Hz, 2H), 5.68 (br s, 1H), 5.58 (br s, 1H), 4.85 (br s, 1H), 3.82 (s, 3H), 1.26 (s, 9H); 13C NMR (150 MHz, CDCl<sub>3</sub>) ppm 161.1, 154.3, 136.2, 134.6, 130.1, 129.1, 128.6, 123.2, 114.3, 93.6, 80.6, 56.1, 55.4, 28.1.

**tert-Butyl (1R,2S)-1-(4-chlorophenyl)-2-nitro-2-(4-nitrophenyl)ethylcarbamate (1m).** Column chromatography (15-30% ethyl acetate in hexanes) afforded a white solid (41.5 mg, 99%) that was found to be 86% ee and 17:1 dr by chiral HPLC; (Chiralcel AD-H, 15% iPrOH/hexanes, 1 mL/min, t<sub>(anti, major)</sub> 27.6 min, t<sub>(anti, minor)</sub> = 14.3 min, t<sub>(syn, major)</sub> = 16.7 min, t<sub>(syn, minor)</sub> = 37.9 min; Mp 165.0-166.0 °C; [α]<sub>D</sub> = -9.1 (c 0.11, CHCl<sub>3</sub>); R<sub>f</sub> = 0.27 (20% EtOAc/hexanes); IR (film) 3405, 2981, 2926, 1681, 1551, 1522 cm<sup>-1</sup>; 1H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.47 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H), 6.92 (d, J = 8.4 Hz, 2H), 5.68 (br s, 1H), 5.58 (br s, 1H), 4.85 (br s, 1H), 3.82 (s, 3H), 1.26 (s, 9H); 13C NMR (150 MHz, CDCl<sub>3</sub>) ppm 161.1, 154.3, 136.2, 134.6, 130.1, 129.1, 128.6, 123.2, 114.3, 93.6, 80.6, 56.1, 55.4, 28.1.

(--)-Nutlin-3 (2).<sup>5</sup> Tf<sub>2</sub>O (28.1 μL, 166.8 μmol) was added to a stirred solution of Ph<sub>3</sub>PO (92.8 mg, 333.6 μmol) in CH<sub>2</sub>Cl<sub>2</sub> (500 μL) at 0 °C. The mixture was stirred for 10 min before urea (50.0 mg, 83.4 μmol) was added as a solution in CH<sub>2</sub>Cl<sub>2</sub> (600 μL), and the reaction was stirred for 1 h at 0 °C. The reaction mixture was allowed to warm to room temperature before addition of aq. NaHCO<sub>3</sub>. The organic layer was separated, the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub>, and the combined organic layers were then dried over MgSO<sub>4</sub>, filtered, and concentrated. Column chromatography (0-4% methanol in dichloromethane) of the residue provided the compound as a white solid (42.5 mg, 88%). Mp 127.0-129.0 °C; [α]<sub>D</sub> = -150 (c 0.13, CHCl<sub>3</sub>); R<sub>f</sub> = 0.24 (5%)

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MeOH/CH₂Cl₂; IR (film) 3229, 2980, 2935, 2247, 1678, 1608 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.59 (d, J = 8.8 Hz, 1H), 7.08 (d, J = 8.4 Hz, 2H), 7.02 (d, J = 8.0 Hz, 2H), 6.92 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.4 Hz, 2H), 6.66 (s, 1H), 6.54 (dd, J = 8.4, 1.6 Hz, 1H), 6.47 (br s, 1H), 5.55 (d, J = 9.6 Hz, 1H), 5.47 (d, J = 9.6 Hz, 1H), 4.60 (qq, J = 6.0, 6.0 Hz, 1H), 3.83 (s, 3H), 3.75 (d, J = 18.0 Hz, 1H), 3.62 (d, J = 18.0 Hz, 1H), 3.40-3.31 (m, 1H), 3.23-3.13 (m, 1H), 2.97 (br s, 2H), 1.37 (d, J = 6.0 Hz, 3H), 1.32 (d, J = 6.0 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) ppm 166.9, 163.0, 160.2, 157.0, 154.7, 136.0, 135.0, 133.1, 132.8, 132.1, 129.2, 128.4, 128.1, 127.9, 113.4, 104.6, 100.1, 71.7, 70.9, 69.1, 55.5, 49.4, 41.8, 40.3, 20.03, 2 0.01; HRMS (CI): Exact mass calcd for C₃₀H₃₁Cl₂N₄O₄ [M+H]⁺ 581.1717, found 581.1705.

This enantiomer corresponded to “enantiomer-a” using the HPLC conditions as described previously. The compound was found to be 99% ee; (Chiralel OD, 30% iPrOH/hexanes, 1 mL/min, tₘajor) = 8.6 min, tₘinor = not observed. Additionally, the (+)-enantioomer was prepared using an identical procedure with (S,S)-H₄PyrrolidineQuin-BAM to form compound 7 (84% ee), which was converted to (+)-Nutlin-3. This compound correlated with “enantiomer-b”. and was found to be 85% ee; (Chiralcel OD, 30% iPrOH/hexanes, 1 mL/min, tₘajor) = 10.5 min, tₘinor = 8.6 min.

Figure 1. Nutlin-3 HMBC Correlations (600 MHz)

Further evidence supporting the structural assignment includes an HMBC (Figure 1), which clearly showed the anticipated couplings for Nutlin-3. C26 (155 ppm) Showed correlations to H27/H27` and H30/H30’ and to H1 (but not H8). C15 (160 ppm) Showed correlations to both of the imidazoline methines (H1 and H8) and also to the H25. See SI-2 for HMBC spectrum.

1-Chloro-4-(nitromethyl)benzene (4). 4-Chlorobenzyl bromide (3.000 g, 14.60 mmol) and phloroglucinol (1.841 g, 14.60 mmol) were dissolved in CH₃CN (32.3 mL) in a round bottom flask at room temperature. The reaction mixture was then chilled to 0 °C before IRA900-ONO (12.4 g, 2.4 equiv.) resin was added. The suspension was then stirred at 0 °C for 70 min and filtered. The resin was rinsed thoroughly with diethyl ether. The filtrate and rinsate were combined and concentrated. Column chromatography of the residue (0-3% ethyl acetate in hexanes) afforded a crystalline solid (1.1642 g, 46%). Mp 28.0-29.0 °C; Rₐ = 0.45 (20% EtOAc/hexanes); IR (film) 3095, 3036, 2916, 1555 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.45-7.35 (m, 4H), 5.41 (s, 2H); ¹³C NMR (100 MHz, CDCl₃) ppm 136.3, 131.4, 129.4, 128.0, 79.1; HRMS (Cl): Exact mass calcd for C₇H₇ClNO₂ [M+H]⁺ 172.0160, found 172.0157.

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**H₆Me-BAM (7).** Pd(dba)₂ (10.1 mg, 17.5 μmol), rac-BINAP (21.8 mg, 35.0 μmol), and sodium tert-butoxide (286.4 mg, 2.98 mmol) were loaded into a round bottom flask in a glove box. Toluene (10 mL, 0.10M) was added to the mixture, followed by (R,R)-diaminocyclohexane (100.0 mg, 876.0 μmol). 2-Bromo-6-methylpyridine (301.5 mg, 1.75 mmol) was added as a solution in toluene. The reaction was allowed to stir at 80 °C and monitored by TLC. The reaction was then cooled to room temperature, concentrated, and purified by flash column chromatography on silica gel (5% triethylamine, 10% ethyl acetate in hexanes) affording a white solid (200 mg, 77%). [α]₂₀° +110 (c 0.10, CHCl₃); mp 126-128 °C; Rᵣ = 0.17 (5% Et₃N, 10% EtOAc/hexanes); IR (neat) 3256, 3051, 2927, 2855, 1559 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.19 (dd, J = 8.0, 8.0 Hz, 2H), 6.35 (d, J = 7.2 Hz, 2H), 6.11 (d, J = 8.4 Hz, 2H), 5.16 (br s, 2H), 3.73-3.64 (m, 2H), 2.37 (s, 6H), 2.27-2.18 (m, 2H), 1.78-1.65 (m, 2H), 1.50-1.28 (m, 4H); ¹³C NMR (100 MHz, CDCl₃) ppm 158.2, 156.5, 137.3, 111.3, 110.4, 55.0, 32.1, 24.4, 24.3; HRMS (ESI): Exact mass calcd for C₁₈H₂₄N₄ [M⁺] 296.2001, found 296.1994.

**H₄PyrrolidineQuin-BAM-HOTf (8a·HOTf).** To a flame-dried vial with stir bar was added H₄PyrrolidineQuin-BAM (8a) (286.3 mg, 565.1 μmol) and dichloromethane (2 mL). Trifluoromethanesulfonic acid (50.0 μL, 565 μmol) was added dropwise to the stirring solution at room temperature. The reaction mixture was allowed to stir an additional 10 minutes before concentration to a light brown solid that was used without further purification. Other catalyst acid salts were made in a similar fashion.

**H₄Pyrrolidine⁶MeOQuin-BAM (8b).** A 2-5 mL microwave vial was charged with H₄Cl⁶OMeQuin-BAM (200 mg, 402 μmol), pyrrolidine (660 μL, 8.041 mmol), and trifluoromethylbenzene (2 mL). This suspension was heated at 220 °C and stirred in the microwave for 20 min. The reaction was then concentrated and purified by column chromatography (5-10% methanol in dichloromethane) to provide a light brown powder. This material was dissolved in dichloromethane and then washed with 3 M aq NaOH. The combined organic layers were dried over MgSO₄ and concentrated to afford a light brown powder (174.4 mg, 77%); [α]₀° +350 (c 0.14, CHCl₃); Rᵣ = 0.29 (10% MeOH/CH₂Cl₂); IR (film) 3261, 2930, 2856, 1595, 1531 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.61 (d, J = 9.2 Hz, 2H), 7.27 (d, J = 2.8 Hz, 2H), 7.11 (dd, J = 8.8, 2.8 Hz, 2H), 5.57 (br s, 2H), 5.35 (s, 2H), 4.03 (br s, 2H), 3.82 (s, 6H), 3.32-3.20 (m, 4H), 3.15-3.05 (m, 4H), 2.32-2.25 (m, 2H), 1.90-1.75 (m, 10H), 1.50-1.30 (m, 4H); ¹³C NMR (100 MHz, CDCl₃) ppm 157.3, 153.0, 152.8, 144.8, 127.5, 118.9, 118.4, 106.0, 94.0, 56.4, 55.6, 51.4, 33.4, 25.4, 25.1; HRMS (ESI): Exact mass calcd for C₃₄H₄₃N₆O₂ [M+H]⁺ 567.3448, found 567.3442.
H[^4]Pyrrolidine[^5]MeOQuin-BAM (8c). A 2-5 mL microwave vial was charged with H[^4]Cl[^7]MeOQuin-BAM (200 mg, 402 μmol), pyrrolidine (660 μL, 8.041 mmol), and trifluoromethylbenzene (2 mL). This suspension was heated at 220 °C and stirred in the microwave for 20 min. The reaction was then concentrated and purified by column chromatography (5-10% methanol in dichloromethane) to provide a light brown solid. This material was dissolved in dichloromethane and then washed with 3 M aq NaOH. The combined organic layers were dried over MgSO₄ and concentrated to afford a light brown powder (123.5 mg, 54%); [α]₀⁺[^20]D +480 (c 0.13, CHCl₃); Rₚ = 0.39 (10% MeOH/CH₂Cl₂); IR (film) 3253, 2930, 2855, 1616, 1589, 1526 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.76 (d, J = 9.0 Hz, 2H), 7.09 (s, 2H), 6.65 (dd, J = 9.5, 2.5 Hz, 2H), 5.77 (br s, 2H), 5.23 (s, 2H), 4.04 (br s, 2H), 3.88 (s, 6H), 3.35-3.25 (m, 4H), 3.20-3.10 (m, 4H), 2.33-2.25 (m, 2H), 1.90-1.78 (m, 10H), 1.55-1.35 (m, 4H); ¹³C NMR (125 MHz, CDCl₃) ppm 159.9, 158.6, 153.2, 151.5, 125.9, 112.7, 110.4, 105.8, 90.7, 56.3, 55.2, 51.5, 33.3, 25.6, 25.0; HRMS (ESI): Exact mass calcd for C₃₄H₄₃N₆O₂ [M+H]⁺ 567.3447, found 567.3467.

H[^4]Pyrrolidine[^6,7](MeO)₂Quin-BAM (8d). A 2-5 mL microwave vial was charged with ⁴Cl[^6,7](MeO)₂Quin-BAM (1.000 g, 1.794 mmol) and pyrrolidine (2.9 mL, 36 mmol). This suspension was heated at 180 °C and stirred in the microwave for 40 min. The reaction was then concentrated and purified by column chromatography (2-5-10% methanol in dichloromethane with 1% AcOH) to provide a light brown solid. This material was dissolved in dichloromethane and then washed with 3 M aq NaOH. The combined organic layers were dried over MgSO₄ and concentrated. The material was then triturated with hexanes to afford a light brown viscous foam (351.1 mg, 31%); [α]₀⁺[^20]D +340 (c 0.11, CHCl₃); Rₚ = 0.22 (10% MeOH/1% AcOH/CH₂Cl₂); IR (film) 3391, 2931, 2855, 1593 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.24 (s, 2H), 7.10 (s, 2H), 5.51 (br s, 2H), 5.37 (s, 2H), 3.99 (br s, 2H), 3.99 (s, 6H), 3.89 (s, 6H), 3.37-3.26 (m, 4H), 3.23-3.13 (m, 4H), 2.35-2.25 (m, 2H), 1.91-1.79 (m, 10H), 1.52-1.38 (m, 4H); ¹³C NMR (100 MHz, CDCl₃) ppm 157.6, 152.8, 151.5, 125.9, 112.7, 110.4, 105.8, 90.7, 146.0, 143.5, 111.7, 106.5, 105.2, 91.9, 56.3, 55.8, 55.5, 51.2, 33.3, 25.3, 25.0; HRMS (CI): Exact mass calcd for C₃₆H₄₃N₆O₄ [M+H]⁺ 627.3653, found 627.3658.
1-Bromo-3-((nitromethyl)benzene (17). NaNO₂ (414.0 mg, 6.00 mmol), urea (721.2 mg, 12.00 mmol), and phloroglucinol (756.7 mg, 6.00 mmol) were stirred with DMF (9.1 mL) at room temperature until homogenous. The reaction mixture was cooled to -20 °C before the addition of bromide (1.4996 g, 6.00 mmol). The mixture was stirred at -20 °C for 5.5 h before being poured into ice water. The mixture was extracted with ether. The combined organic extracts were washed with water, dried over MgSO₄, filtered, and concentrated. Column chromatography (0-10% EtOAc/hexanes) provided a clear, slightly green oil (379.9 mg, 29%). R_f = 0.23 (10% EtOAc/hexanes); IR (film) 3064, 2914, 1553 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 7.64-7.61 (m, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.40 (d, J = 7.8 Hz, 1H), 7.32 (dd, J = 7.8, 7.8 Hz), 5.40 (s, 2H); ¹³C NMR (150 MHz, CDCl₃) ppm 133.2, 133.0, 131.4, 130.6, 128.6, 122.9, 79.1; HRMS (CI): Exact mass calcd for C₇H₆BrNO₂ [M⁺] 214.9576, found 214.9575.

2-(Nitromethyl)naphthalene (18). NaNO₂ (1.035 g, 15.00 mmol), urea (1.202 g, 20.00 mmol), phloroglucinol (1.261 g, 10.00 mmol), and bromide (2.211 g, 10.00 mmol) were reacted according to the aforementioned procedure but with a reaction time of 5 h. Column chromatography (0-3% EtOAc/hexanes) provided a yellow solid (358.4 mg, 19%). Mp 81.5-82.5 °C. R_f = 0.30 (10% EtOAc/hexanes); IR (film) 3060, 2910, 1550 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 7.94-7.85 (m, 4H), 7.59-7.52 (m, 3H), 5.60 (s, 2H); ¹³C NMR (150 MHz, CDCl₃) ppm 133.6, 133.0, 130.0, 129.0, 128.2, 127.8, 127.2, 127.0, 126.8, 126.4, 80.2; HRMS (CI): Exact mass calcd for C₁₁H₉NO₂ [M⁺] 187.0628, found 187.0634.

2-Isopropoxy-4-methoxybenzoic acid (21).³ Ester (985.0 mg, 3.904 mmol) was boiled with KOH (703.8 mg, 12.54 mmol) in a mixture of ethanol (11.7 mL) and water (2.3 mL) for 4 h. EtOH was then removed by evaporation. The remaining material was diluted with water and treated with 3 M HCl until precipitation occurred. The suspension was then extracted with diethyl ether. The combined organic layers were washed with brine before drying over MgSO₄. The solution was concentrated to a red oil (733.2 mg, 89%) that was pure by ¹H NMR. R_f = 0.33 (50% EtOAc/hexanes); IR (film) 3261, 2981, 1730, 1608 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 10.91 (br s, 1H), 8.12 (d, J = 9.0 Hz, 1H), 6.62 (dd, J = 9.0, 2.5 Hz, 1H), 6.52 (d, J = 2.0 Hz, 1H), 4.81 (heptet, J = 6.5 Hz, 1H), 3.86 (s, 3H), 1.47 (d, J = 6.0 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) ppm 165.5, 164.9, 157.8, 135.4, 111.4, 106.8, 100.7, 73.9, 55.7, 21.9; HRMS (ESI): Exact mass calcd for C₁₁H₁₄NaO₄ [M+Na⁺] 233.0790, found 233.0795.
**tert-Butyl (1R,2S)-1,2-bis(4-chlorophenyl)-2-(2-isoproxy-4-methoxybenzamido)ethylcarbamate (22).**

The amine (170.0 mg, 445.8 μmol) and carboxylic acid (93.7 mg, 445.8 μmol) were dissolved in CH₂Cl₂ (2.2 mL) at room temperature. The solution was chilled to 0 °C and EDC (111.1 mg, 579.6 μmol) and DMAP (5.4 mg, 44.6 μmol) were added. The reaction mixture was stirred and allowed to gradually warm to room temperature. After 16 h, the reaction mixture was diluted with water and extracted with CH₂Cl₂. The combined organic layers were washed once with water, dried over MgSO₄, and concentrated. The resulting white solid was washed with CH₂Cl₂ and hexanes, leaving a white solid (224.5 mg, 88%) that was pure by NMR. Mp 239.0-241.0 °C (decomp); [α]²⁰_D -29 (c 0.13, CHCl₃); R₉ = 0.13 (20% EtOAc/hexanes); IR (film) 3355, 2976, 1680, 1629, 1607, 1529 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.39 (d, J = 7.2 Hz, 1H), 8.19 (d, J = 8.8 Hz, 1H), 7.26 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 7.02 (d, J = 6.8 Hz, 2H), 6.93 (d, J = 8.4 Hz, 2H), 6.59 (dd, J = 8.8, 2.4 Hz, 1H), 6.46 (d, J = 1.6 Hz, 1H), 5.91 (br s, 1H), 5.78 (br s, 1H), 5.07 (br s, 1H), 4.75-4.60 (m, 1H), 3.84 (s, 3H), 1.38 (s, 9H), 1.30-1.21 (m, 6H); ¹³C NMR (100 MHz, CDCl₃) ppm 165.6, 163.6, 157.2, 155.0, 136.9, 136.7, 134.2, 133.6, 128.6 (2C), 128.5, 128.3, 114.1, 105.2, 100.2, 79.9, 71.4, 59.5, 56.6, 55.5, 28.3, 22.0, 21.6; HRMS (ESI): Exact mass calcd for C₃₀H₃₄Cl₂N₂NaO₅ [M+Na]⁺ 595.1742, found 595.1743.

**2-Oxo-piperazine (23).**

The resulting orange oil was purified by column chromatography (10% MeOH in CH₂Cl₂ w/ 1% NH₄OH). A yellow solid (2.8634 g, 71%) was obtained that was sufficiently pure by ¹H NMR. R₉ = 0.07 (10% MeOH/CH₂Cl₂ w/ 1% NH₄OH); IR (film) 3400, 1650 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.18 (br s, 1H), 3.46 (s, 2H), 3.35-3.28 (m, 2H), 2.98 (t, J = 5.5 Hz, 2H), 1.89 (br s, 1H); ¹³C NMR (125 MHz, CDCl₃) ppm 170.4, 49.6, 42.7, 42.2; HRMS (CI): Exact mass calcd for C₄H₉N₂O [M+H]⁺ 101.0709, found 101.0714.

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Catalytic, Enantioselective Synthesis of Stilbene cis-Diamines:
A Concise Preparation of (-)-Nutlin 3, a Potent p53-MDM2 Inhibitor

Tyler A. Davis and Jeffrey N. Johnston*

Department of Chemistry & Vanderbilt Institute of Chemical Biology
Vanderbilt University
2301 Vanderbilt Place, Nashville, TN 37235-1822

Figure 35. 13C NMR (100 MHz, CDCl3) of Figure 25. 13C NMR (150 MHz, CDCl3) of Figure 23. 13C NMR (150 MHz, CDCl3) of Figure 21. 13C NMR (100 MHz, CDCl3) of Figure 11. 13C NMR (125 MHz, CDCl3) of Figure 38. 1H NMR (400 MHz, CDCl3) of Figure 33. 13C NMR (150 MHz, CDCl3) of Figure 32. 1H NMR (600 MHz, CDCl3) of Figure 31. 13C NMR (150 MHz, CDCl3) of Figure 30. 1H NMR (600 MHz, CDCl3) of Figure 27. 13C NMR (150 MHz, CDCl3) of Figure 26. 1H NMR (600 MHz, CDCl3) of Figure 22. 1H NMR (400 MHz, CDCl3) of Figure 18. 1H NMR (400 MHz, CDCl3, 330 K) of Figure 17. 13C NMR (100 MHz, CDCl3, 325 K) of Figure 16. 1H NMR (500 MHz, CDCl3, 325 K) of Figure 15. 13C NMR (100 MHz, CDCl3) of Figure 14. 1H NMR (400 MHz, CDCl3) of Figure 13. 13C NMR (150 MHz, CDCl3, 325 K) of Figure 12. 1H NMR (600 MHz, CDCl3, 325 K) of Figure 11. 13C NMR (125 MHz, CDCl3) of Figure 10. 1H NMR (500 MHz, CDCl3) of Figure 9. 13C NMR (100 MHz, CDCl3) of Figure 8. 1H NMR (400 MHz, CDCl3) of Figure 7. 13C NMR (100 MHz, CDCl3) of Figure 6. 1H NMR (400 MHz, CDCl3) of Figure 5. 13C NMR (100 MHz, CDCl3) of Figure 4. 1H NMR (400 MHz, CDCl3) of Figure 3. Crystal Structure of Figure 2. 13C NMR (150 MHz, CDCl3) of Figure 1. 1H NMR (400 MHz, CDCl3) of

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![NMR Spectrum of 1k](image-url)
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C26 (155 ppm) showed correlations to H27/H27' and H30/H30' and to H1 (but not H8). C15 (160 ppm) showed correlations to both of the imidazoline methines (H1 and H8) and also to the H25.
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![Figure 61: $^{13}$C NMR spectrum of 8d](image_url)

**Supplementary Material (ESI) for Chemical Science**

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