Supporting Information

Synthesis of Biologically Active Amines via Rhodium-Bisphosphite Catalyzed Hydroaminomethylation

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General. Reagents were purchased from Aldrich. The 6,6'-[[3,3',5,5'-tetrakis(1,1-dimethylethyl)[1,1'-biphenyl]-2,2'-diyl]bis(oxy)]bis-dibenzo[d,f][1,3,2]dioxaphosphepin **1a** was prepared as described previously.[1]. NMR spectra were obtained using a Varian INOVA 300 MHz NMR. High-resolution electrospray mass spectra were obtained using a Micromass Qtof-2 mass spectrometer. Low-resolution GC-MS data were obtained using a DB-1 column on a Hewlett-Packard 6890 gas chromatograph equipped with a HP5973 mass selective detector. Combustion analyses were performed by Galbraith Laboratories.

General procedure for hydroaminomethylation of 1-pentene with piperidine. Reaction mixtures were prepared by addition of ligand and $Rh(CO)_2(acac)$ stock solutions to THF solvent followed by addition of pentene solution and piperidine. Total amount of liquids in each reactor cell was 4.5 mL. Ligand solutions (0.03 M for **1a** and 0.06 M for **1b**) and $Rh(CO)_2(acac)$ (0.05 M) were prepared in the dry box by dissolving appropriate amount of compound in toluene at room temperature. 1-Pentene solution was prepared by mixing 8.285 g of pentene and 5.220 g of decane (as a GC internal standard) (1:0.31 molar ratio). Hydroaminomethylation reactions were conducted in an Argonaut Endeavor® reactor system housed in an inert atmosphere glove box. The reactor system consists of eight parallel, mechanically stirred pressure reactors with individual temperature and pressure controls. Upon charging the catalyst solutions, the reactors were pressurized with 400 psi of syn gas (CO/H_2 1:2) and then heated to 90 °C while stirring at 800 rpm. After 18 hrs reactors were cooled, vented and purged with nitrogen. Upon opening the reactor 0.1 mL of each reaction mixture was taken out and diluted with 1.6 mL of toluene, and this solution was analyzed by gas chromatography (Supelco Beta Dex 225).

Synthesis of 2-(4-nitrophenyl)-1,3-dioxolane. 4-Nitrobenzaldehyde (6.60 g, 43.67 mmol) and *p*-toluenesulfonic acid monohydrate (153 mg, 0.804 mmol) were dissolved in 150 mL of toluene. Ethylene glycol (5 mL) was added, and the solution was refluxed with a Dean-Stark trap to azeotropically remove water. After 1 hour, the solution was allowed to cool to ambient temperature and 100 mL of Et_2O was added. The solution was washed twice with saturated $NaHCO_3$ solution and then with saturated NaCl solution. The solution was dried ($MgSO_4$) and evaporated to yield a yellow solid (8.13 g, 95% yield). ^{1}H NMR (acetone-d_6) δ 8.23 (d, ^3J = 8.7 Hz, 2H, aromatic C*H*), 7.71 (d, ^3J = 8.7 Hz, 2H, aromatic C*H*), 5.86

[1] Billig, E.; Abatjoglou, A.G.; Bryant, D.R. US Pat. 4,668,651, 1988.

(s, 1H, C*H*O_2), 4.03 (m, 4H, OC*H_2*). $^{13}C\{^1H\}$ NMR (acetone-d_6) δ 149.3 (q), 146.6 (q), 128.6 (aromatic *C*H), 124.2 (aromatic *C*H), 102.9 (*C*HO_2), 66.2 (O*C*H_2).

Synthesis of 4-(1,3-dioxolan-2-yl)-benzenamine. PtO_2 (502 mg, 2.21 mmol) and $MgSO_4$ (7.34 g, 61.0 mmol) were added to a solution of 2-(4-nitrophenyl)-1,3-dioxolane (5.93 g, 30.4 mmol) in 60 mL of THF. The resulting suspension was stirred under 70 psi H_2 in a 25 mL Parr reactor for 5 h. Solids were removed by filtration, and the filtrate was evaporated to give a golden liquid (5.13 g, 51% yield). ^1H NMR (acetone-d_6) δ 7.15 (d, ^3J = 8.4 Hz, 2H, aromatic C*H*), 6.62 (d, ^3J = 8.4 Hz, 2H, aromatic C*H*), 5.55 (s, 1H, C*H*O_2), 4.7 (br s, 2H, N*H_2*), 3.95 (m, 4H, OC*H_2*). $^{13}C\{^1H\}$ NMR (acetone-d_6) δ 150.12 (q), 128.64 (aromatic *C*H), 127.21 (q), 114.47 (*C*HO_2), 65.59 (O*C*H_2).

Synthesis of N-(4-formylphenyl)-methanesulfonamide (2). 4-(1,3-Dioxolan-2-yl)-benzenamine (1.793 g, 10.86 mmol) was dissolved in 25 mL CH_2Cl_2 and cooled to 0 ºC. Pyridine was added (925 mg, 11.7 mmol). Methanesulfonyl chloride (1.369 g, 11.9 mmol) was added dropwise over 30 min, and the solution was allowed to warm to room temperature with stirring. After 16 h, 6 M NaOH (5 mL) was added followed by 150 mL of water. The aqueous layer was separated, washed with 50 mL CH_2Cl_2 and then acidified to pH 1 with 2M HCl. The resulting suspension was extracted into ethyl acetate (4 x 50 mL) which was subsequently dried ($MgSO_4$) and evaporated to give **2** as a yellow solid (920 mg, 42% yield, 20% overall yield from 4-nitrobenzaldehyde). ^1H NMR (acetone-d_6) δ 9.94 (s, 1H, C*H*O), 9.20 (br s, 1H, $MeSO_2$N*H*), 7.90 (d, ^3J = 8.7 Hz, 2H, aromatic C*H*), 7.48 (d, ^3J = 8.7 Hz, 2H, aromatic C*H*), 3.14 (s, 3H, *Me*SO_2). $^{13}C\{^1H\}$ NMR (acetone-d_6) δ 191.60 (*C*HO), 145.12 (q), 133.10 (q), 132.08 (aromatic *C*H), 119.05 (aromatic *C*H), 40.24 (*Me*SO_2). HRMS calcd for $C_8H_9NO_3S$: 199.030, Found: 199.031. Anal. calcd. for $C_9H_9NO_3S$: C, 48.23; H, 4.55; N, 7.03. Found C, 48.05; H, 4.62; N, 6.59.

Alternate synthesis of N-(4-formylphenyl)-methanesulfonamide (2) by Pd-catalyzed coupling. Methanesulfonamide (789 mg, 8.29 mmol), cesium carbonate (3.35 g, 10.3 mmol), palladium(II) acetate (140 mg, 0.624 mmol) and Xantphos (598 mg, 1.03 mmol) were suspended in 25 mL of anhydrous 1,4-dioxane. 4-Bromobenzaldehyde (1.200 g, 6.485 mmol) was added, and the reaction mixture was heated at 90 °C for 18 h. The solution was cooled to room temperature and washed with 10% HCl (80 mL). The organic layer was extracted with 2 M NaOH (2 x 75 mL). The combined aqueous extracts were neutralized with concentrated HCl, and product was then extracted into CH_2Cl_2 (2 x 50 mL). The organic extracts were washed with brine, dried (Na_2SO_4) and evaporated to a yellow powder. The solid was extracted with boiling acetone and the resulting solution was cooled to –35 °C to give a white solid. The supernatant was decanted and evaporated to a yellow solid whose spectral properties were identical to material prepared by the preceding method (343 mg, 26% yield).

Synthesis of N-[4-(1-Hydroxy-allyl)-phenyl]-methanesulfonamide (3). A solution of (4-formylphenyl)-methanesulfonamide (**2**) (834 mg, 4.19 mmol) in 13 mL of THF was added to 8.5 mL (8.5 mmol) of 1.0 M ($H_2C=CH_2$)MgBr in THF. The resulting suspension was stirred for 3.5 h and then quenched with 10 mL of saturated NH_4Cl solution. The solution was extracted with Et_2O (2 x 20 mL) and separated. The combined organic extracts were washed with water and saturated NaCl solution. After drying ($MgSO_4$), the solution was evaporated to give an orange liquid (1.036 g). ^{1}H NMR (acetone-d_6) δ 8.52 (br s, 1H, CH_3SO_2NH), 7.31 (AB quartet, J = 8.7 Hz, 4H, aromatic C*H*), 5.99 (ddd, J = 6.3, 10.8, 16.8 Hz, C*H*=CH_2, 1H), 5.29 (td, J = 1.7, 16.8 Hz, 1H, trans CH=C*H*H), 5.15 (d, 6.3 Hz, C*H*(OH), 1H), 5.06 (td, J = 1.4, 10.8 Hz, 1H, cis CH=C*H*H), 4.57 (br s, 1H, O*H*), 2.94 (s, 3H, CH_3SO_2). ^{13}C{^{1}H} NMR (acetone-d_6) δ 142.39 (*C*H=CH_2), 141.09 (q), 138.03 (q), 128.10 (aromatic *C*H), 121.11 (aromatic *C*H), 114.10 (CH=*C*H_2), 74.73 (*C*H(OH)), 39.25 (*C*H_3SO_2). HRMS calcd for $C_{10}H_{13}NO_3S$: 227.062, Found: 227.062. Anal. calcd. for $C_{10}H_{13}NO_3S$: C, 52.85; H, 5.77; N, 6.16. Found C, 53.02; H, 6.16; N, 6.00.

Synthesis of N-heptyl-acetamide. This compound was prepared by a modification of a published procedure.[2] A solution of *n*-heptylamine (10.31 g, 89.4 mmol) in 100 mL CH_2Cl_2 was cooled in an ice bath. Pyridine (7.5 mL, 92.7 mmol) was added. Acetyl chloride (8.0 mL, 11 mmol) was gradually added over the course of 2 min. The ice bath was removed and the solution was allowed to warm to room temperature. After 1 h, water (100 mL) was added, and the organic layer was separated. The aqueous layer was extracted with 100 mL CH_2Cl_2. The combined organic extracts were washed with 10% aqueous HCl solution, saturated $NaHCO_3$ solution and then saturated NaCl solution. The solution was dried ($MgSO_4$) and evaporated to a colorless liquid (13.73 g, 98% yield). ^{1}H NMR ($CDCl_3$) δ 6.97 (br s, 1H, N*H*Ac), 3.02 (q, ^3J = 7.2 Hz, 2H), 1.80 (s, 3H, CO CH_3), 1.32 (m, 2H), 1.10 (m, 8H), 0.69 (t, ^3J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$) δ 170.27 (*C*O CH_3), 39.34, 31.41, 29.15, 28.67, 26.62, 22.64 (CO *C*H_3), 22.23, 13.68 (heptyl *C*H_3). HRMS calcd for $C_9H_{19}NO$: 157.147, Found: 157.147.

Synthesis of N-ethyl-1-heptanamine A solution of *n*-heptyl acetamide (6.076 g, 38.63 mmol) in 6 mL of Et_2O was added dropwise to a suspension of $LiAlH_4$ (4.60 g, 0.121 mol) in 150 mL Et_2O. The suspension was refluxed for 8 h, cooled in ice and quenched with 4 mL H_2O, 4 mL of 2M NaOH and 12 mL of H_2O. The resulting suspension was filtered and the filtrate dried (Na_2SO_4). Evaporation of solvent gave a colorless liquid (5.29 g, 95% yield). ^{1}H NMR ($CDCl_3$) δ 2.47 (q, ^3J = 7.2 Hz, 2H, NC$H_2$$CH_3$), 2.42 (t, ^3J = 7.5 Hz, 2H, heptyl NCH_2), 1.31 (m, 4H), 1.12 (m, 8H), 0.94 (t, ^3J = 7.2 Hz, 3H, NCH_2CH_3), 0.71 (t, ^3J = 7.2 Hz, 3H, heptyl CH_3). ^{13}C{^{1}H} NMR ($CDCl_3$) δ 49.70 (heptyl N*C*H_2), 43.90 (N*C*H_2CH_3), 31.56, 29.93, 29.00, 27.13, 22.34, 15.00 (NCH_2CH_3), 13.76 (heptyl *C*H_3). HRMS calcd for $C_9H_{21}N$: 143.167, Found: 143.169.

[2] Fitch, W. L.; Baer, T. A.; Chen, W.; Holden, F.; Holmes, C. P.; Maclean, D.; Shah, N.; Sullivan, E.; Tang, M.; Waybourn, P.; Fischer, S. M.; Miller, C. A.; Snyder, L. R. *J. Comb. Chem.* **1999**, *1*, 188-194.

Synthesis of Ibutilide. $Rh(CO)_2(acac)$ (6.9 mg, 27 μmol) and bisphosphite **1a** (25.0 mg, 29.8 μmol) were dissolved in 3 mL THF under nitrogen. The solution was transferred to a mechanically stirred 25 mL Parr autoclave and stirred under 400 psi of 1:1 H_2/CO for 30 min. A solution of **3** (438 mg, 1.93 mmol) and (n-C_7H_{15})$N(H)C_2H_5$ (283 mg, 1.97 mmol) in 3 mL of THF was injected into the reactor against a flow of H_2/CO. The reactor was heated at 75 ºC under 400 psi of 1:1 CO/H_2 After 18 h, the reactor was cooled to ambient temperature and vented. The reaction mixture was evaporated and redissolved in CH_2Cl_2 (20 mL). Product was extracted into 2M NaOH (2 x 15 mL). The aqueous layer was then neutralized with 10% HCl and then extracted with CH_2Cl_2 (3 x 10 mL). The organic layer was dried ($MgSO_4$) and evaporated to give product as an orange liquid (410 mg, 55% yield). GC-MS indicated the product consisted of a mixture of Ibutilide and a branched isomer (linear/branched = 48). ^{1}H NMR (acetone-d_6) δ 7.33 (AB quartet, J = 9.0 Hz, 4H, aromatic C*H*), 4.63 (m, 1H, (HO)C*H*), 2.92 (s, 3H, CH_3SO_2), 2.9 (m, 4H), 1.66 (m, 6H), 1.29 (m, 8H), 1.12 (t, ^3J = 7.8 Hz, 3H, NCH_2CH_3), 0.87 (t, ^3J = 7.2 Hz, 3H, heptyl CH_3). $^{13}C\{^1H\}$ NMR (acetone-d_6) δ 143.62 (q), 137.84 (q), 127.53 (aromatic *C*H), 121.32 (aromatic *C*H), 73.22 (*C*-OH), 53.80, 53.39, 47.75, 39.19, 38.92 (CH_3SO_2), 32.54, 27.96, 26.19, 23.55, 23.28, 14.43 (CH_3), 10.73 (CH_3). HRMS (PCI/NH_3) calcd for $C_{20}H_{35}N_2O_2S$ (m + H - H_2O): 367.242, Found: 367.244.

Synthesis of Aripiprazole. $Rh(CO)_2(acac)$ (4.7 mg, 18 μmol) and bisphosphite **1a** (19.7 mg, 23 μmol) were dissolved in 3 mL THF under nitrogen. The solution was transferred to a mechanically stirred 25 mL Parr autoclave and stirred under 400 psi of 1:1 CO/H_2 for 30 min. A solution of 1-(2,3-dichlorophenyl)piperazine[3] (616 mg, 2.66 mmol) and 7-(allyloxy)-3,4-dihydro-2(1*H*)-quinoline (547 mg, 2.69 mmol) in 7 mL of THF was injected into the reactor against a flow of H_2/CO. The reactor was heated at 75 ºC under 400 psi of 1:1 H_2/CO. After 16 h, the reactor was cooled to ambient temperature and vented. The reaction mixture was evaporated and redissolved in 10 mL of $CHCl_3$. The solution was washed with 10% HCl solution, saturated $NaHCO_3$ solution and then saturated NaCl solution. After drying ($MgSO_4$), the solution was evaporated to an orange oil which was crystallized from MeOH (731 mg, 67% yield). The ^{1}H NMR spectrum of the product was identical to that reported by Oshiro, *et al*.[4] ^{1}H ($CDCl_3$) δ 8.47 (s, N*H*CO, 1H), 7.04 (d, *J* = 8.0 Hz, aromatic, 1H), 6.95 (m, aromatic C*H*, 1H), 6.52 (dd, *J* = 2.5, 8.0 Hz, aromatic C*H*, 1H), 6.35 (d, *J* = 2.5 Hz, H8, 1H), 3.97 (t, *J* = 6.0 Hz, OCH_2, 2H), 3.07 (m, 4H), 2.90 (t, *J* = 7.0 Hz, 2H), 2.62 (m, 6H), 2.48 (t, *J* = 7.0 Hz, 2H), 1.76 (m, 4H). $^{13}C\{^1H\}$ (acetone-d_6) δ 171.0 (NH*C*O), 159.6, 152.5, 140.4, 134.2, 129.4, 129.1, 125.3, 120.2, 116.6, 108.7, 102.8, 68.4, 58.5, 53.9, 52.0, 31.8, 27.9, 25.4, 23.8. HRMS (electrospray) calcd for $C_{23}H_{27}N_3O_2Cl_2$ (m + H): 448.156, Found: 448.157.

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[3] Morita, S.; Kitano, K.; Matsubara, J.; Ohtani, T.; Kawano, Y.; Otsubo, K.; Uchida, M. *Tetrahedron* **1998**, *54*, 4811-4818.

[4] Oshiro, Y.; Sato, S.; Kurahashi, N.; Tanaka, T.; Kikuchi, T.; Tottori, K.; Uwahodo, Y.; Nishi, T., *J. Med. Chem.* **1998**, *41*, 658-667.