Synthesis and Structural Characterization of Cross-Linked Histidine-Phenol Cu(II) Complexes as Models for the Active Site of Cytochrome *c* Oxidase

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Supporting Information, Part 1: Detailed Experimental Procedures and X-ray of ***5***

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General Experimental. Melting point determinations are uncorrected. Infrared spectra were recorded as thin films on salt plates or KBr pellet, as indicated, with ν_{max} in inverse centimeters. Proton (^{1}H NMR) and carbon (^{13}C NMR) magnetic resonance spectra were obtained in $CDCl_3$ at 500 MHz and 125 MHz respectively (unless otherwise noted). NMR shifts are reported as delta (δ) units in parts per million (ppm) and coupling constants (*J*) are reported in Hertz (Hz). The following abbreviations were utilized to describe peak patterns when appropriate: br=broad, s=single, d=doublet, t=triplet, q=quarter, and m=multiplet. High resolution mass measurements were obtained on an ESITOF mass spectrometer.

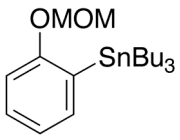
All air and moisture sensitive reactions were carried out under an atmosphere of dry argon using oven-dried or flame-dried glassware and standard syringe techniques. Tetrahydrofuran was distilled from sodium/benzophenone. Dichloromethane and triethylamine were distilled from CaH_2. Methanol was distilled over magnesium tunings. Anhydrous chloroform was used as received. $Pb(OAc)_4$ was dried over solid KOH under vacuum for 3 h before use.

Flash chromatography was performed on Merck 60, 40-75 mesh silica gel using EtOAc-hexane mixtures as solvent unless otherwise indicated. Thin layer chromatography (TLC) was carried out on Whatman silica gel plates with UV detection.

Ground-state UV-visible spectra of the ligands and their Cu-complexes were recorded in a 8:2 mixture of 10 mM Tris-HCl (pH 8.5) and acetonitrile at room temperature on a Hewlett–Packard (8452) diode array spectrophotometer. The time-resolved optical absorption difference spectra were recorded as described previously[1,2,3] using an optical multichannel analyzer at 12 delay times between 100 ns and 500 μs following excitation at 266 nm (Nd:YAG, 7 ns pulse, 15 mJ/pulse). Each spectrum is an average of 20 individual spectra. The time-resolved difference

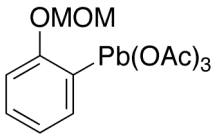
spectra were analyzed by singular value decomposition (SVD) and global exponential fitting using Matlab (The Mathworks) as previously described[1-3].

Spectrophotometric titrations of the ligands and Cu-complexes were recorded on the HP diode array spectrophotometer over a wide spectral and pH ranges. The samples were in prepared in aqueous solution of 0.1 M KCl. The pK_a values of the complexes were extracted using SVD and global pK_a fitting as previously described.[1]



Tributyl[(2-methoxymethoxy)phenyl]tin:[4]

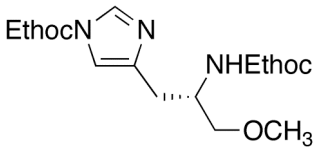
1-Bromo-2-methoxymethoxybenzene[5] (28.93 mmol) was dissolved in anhydrous THF (289 mL) and cooled to -78 ˚C. *n*-BuLi (13.0 mL, 34.70 mmol) was added drop-wise, followed by the slow addition of Bu_3SnCl (10.2 mL, 37.61 mmol). The reaction was allowed to warm to rt over 1 h at which time the reaction mixture was concentrated *in vacuo*. The resulting mixture was partitioned between hexanes and CH_3CN. The hexanes layer was separated and washed once more with CH_3CN. The hexane layers were combined and concentrated *in vacuo* to yield MOM-protected 2-tributyl tin phenol (12.238 g, 99.2% over two steps). IR (thin film) 2955.3, 1464.7, 1007.5, 756.5 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (dd, 1H, *J* = 1.7 Hz, *J* = 7.0 Hz), 7.27 (m, 1H), 7.06 (d, 1H, *J* = 8.2 Hz), 6.99 (dt, 1H, *J* = 0.9 Hz, *J* = 7.2 Hz), 5.15 (s, 2H), 3.46 (s, 3H), 1.55 (m, 6H), 1.31 (m, 6H), 1.05 (m, 6H), 0.86 (m, 9H); ^{13}C-NMR (500 MHz, $CDCl_3$) δ 163.5, 137.2, 129.9, 122.1, 112.3, 94.3, 56.1, 29.4, 27.6, 13.9, 10.0.



Triacetoxy[(2-methoxymethoxy)phenyl]lead (9):

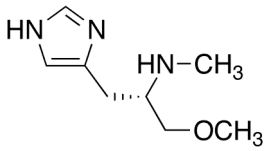
$Hg(CO_2CF_3)_2$ (2.12 g, 4.97 mmol) was added to Tributyl[(2-methoxymethoxy)phenyl]tin (21.23 g, 49.70 mmol) dissolved in $CHCl_3$ (497 mL). $Pb(OAc)_4$ that had previously been dried *in vacuo* in darkness for 3 h was added in one portion. The reaction

was heated to 40 ˚C for 18 h. Activated carbon (25 g) was added and the reaction was filtered through celite. The filtrate was concentrated *in vacuo* and covered with a layer of hexanes. The heterogeneous mixture was stirred for 2 h and the hexanes layer was decanted carefully. The very pale yellow to white solid was again covered with hexanes and this time allowed to stir for 18 h. The hexanes layer was decanted and the solid was dried *in vacuo* to yield triacetoxy[(2-methoxymethoxy)phenyl]lead **9** (20.377 g, 79%). IR (KBr pellet) 2954.6, 1567.8, 1400.6, 979.6, 690.3 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (dd, 1H, *J* = 1.4 Hz, *J* = 8.0 Hz), 7.44 (dt, 1H, *J* = 1.5 Hz, *J* = 7.5 Hz), 7.29 (dd, 1H, *J* = 1.3 Hz, *J* = 8.2 Hz), 7.24 (ddd, 1H, *J* = 1.3 Hz, *J* = 7.3 Hz, *J* = 8.0 Hz), 5.22 (s, 2H), 3.50 (s, 3H), 2.10 (s, 9H); ^{13}C-NMR (500 MHz, $CDCl_3$) δ 180.1, 163.5, 155.7, 151.2, 133.4, 131.9, 124.6, 115.7, 95.1, 56.7, 20.4.



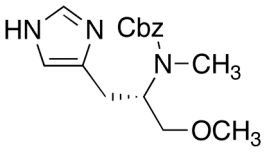
Ethoc-(*L*)-His(Ethoc)-OMe:

L-Histidinol methyl ether dihydrochloride (**6**, 1.026 g, 4.50 mmol) was placed in a flask with CH_2Cl_2 (45 mL) and cooled to 0 ˚C. Et_3N (2.5 mL, 17.99 mmol) was added slowly followed by drop-wise addition of ethyl chloroformate (0.9 mL, 9.45 mmol). The reaction was stirred for 18 h and then washed twice with H_2O. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to afford Ethoc-(*L*)-His(Ethoc)-OMe (1.386 g, >99 %). IR (thin film) 2983.4, 1694.7, 1249.6, 771.5; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.16 (s, 1H), 5.51 (d, 1H, *J* = 6.3 Hz), 4.40 (q, 2H, *J* = 7.1 Hz), 4.04 (m, 3H), 3.35 (dd, 1H, *J* = 4.4 Hz, *J* = 9.3 Hz), 3.28 (s, 3H), 3.25 (dd, 1H, *J* = 5.8 Hz, *J* = 9.4 Hz), 2.77 (d, 2H, *J* = 5.8 Hz), 1.38, (t, 3H, *J* = 7.1 Hz), 1.16 (t, 3H, *J* = 7.1 Hz); ^{13}C-NMR (500 MHz, $CDCl_3$) δ 156.3, 148.6, 140.5, 136.8, 114.4, 73.2, 64.4, 60.6, 59.0, 50.1, 29.6, 14.6, 14.2; $[\alpha]^{23}_{D}$= 3.2° (*c* = 1.1 in MeOH); HRMS calc'd for $C_{13}H_{22}N_3O_5$ [M+H], 300.15540, found 300.15434.



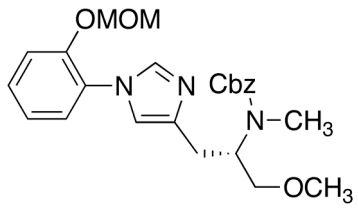
***N*-Methyl-(*L*)-histidinol methyl ether (7):**

Ethoc-(*L*)-His(Ethoc)-OMe (9.93 g, 13.14 mmol) was dissolved in THF (55 mL) and added to a solution of $LiAlH_4$ (2.99 g, 78.84 mmol) in THF (55 mL) at 0 ˚C. After refluxing for 18 h, the solution was cooled to 0 ˚C and H_2O (3.0 mL), 15% NaOH (3.0 mL), and H_2O (9.0 mL) were added drop-wise in that order. After stirring for 30 min, the solution was filtered through filter paper, taking care to get all the lithium salts into the paper. The paper containing the solid was placed in a soxhlet extractor and extracted with the filtrate THF. After 48 h, the liquid was concentrated to yield *N*-methyl-(*L*)-histidinol-methyl ester (**7**) (2.306 g, >99%). IR (thin layer) 2888.8, 1660.4, 1457.1, 1115.7; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (s, 1H), 6.76 (s, 1H), 3.36 (ddd, 1H, J = 2.1 Hz, J = 4.3 Hz, J = 9.3 Hz), 3.30 (s, 3H), 3.25 (ddd, 1H, J = 1.0 Hz, J = 6.3 Hz, J = 9.5 Hz), 2.91 (m, 1H), 2.76 (dd, 1H, J = 4.0 Hz, J = 15.0 Hz), 2.69 (dd, 1H, J = 6.3 Hz, J = 15.0 Hz), 2.43 (s, 3H); ^{13}C-NMR (500 MHz, $CDCl_3$) δ 134.6, 74.0, 59.2, 59.1, 33.9, 26.8; $[\alpha]^{23}_D$= 15.3° (*c* = 0.3 in MeOH); HRMS calc'd for $C_8H_{16}N_3O$ [M+H], 170.12879, found 170.12806.



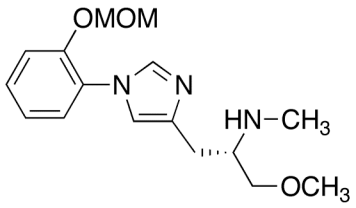
_N_-Carbobenzyloxy-_N_-methyl-(_L_)-histidinol methyl ether (8):

N-Methyl-(*L*)-histidinol methyl ether (**7**) (16.751 g, 9.90 mmol) was dissolved in CH_2Cl_2 (98.9 mL). Et_3N and then Z-succinate were added. The mixture was allowed to react in an inert atmosphere for 18 h and then washed twice with H_2O (100 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to afford the bis Z-protected *L*-histidinol. The bis Z-protected *L*-histidinol was then taken up in $PrNH_2$ (0.990 mol, 84 mL) stirred for 2.5 h, and then concentrated *in vacuo* to afford *N*-carbobenzyloxy-*N*-methyl-(*L*)-histidinol-methyl ether. This compound was used without purification.



2-(_S_)-[(Benzyloxycarbonyl)methylamino]-3-{1-[2-(methoxymethoxy)phenyl]-imidazol-4-yl}-propyl methyl ether (10):

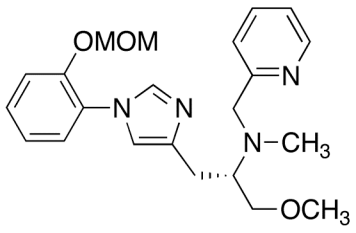
N-Carbobenzyloxy-*N*-methyl-(*L*)-histidinol methyl ether **8** (3.69 mmol) was dissolved in CH_2Cl_2 (37 mL). $Cu(OAc)_2$ (67 mg, 0.37 mmol) followed by aryllead (IV) reagent (**9**) (2.69 g, 5.16 mmol) were added. The reaction was allowed to proceed for 18 h at rt under an inert atmosphere. After several hours, a white precipitate was observed. A 20% aqueous Na_2S solution (40 mL) was added. The resulting black heterogeneous solution was filtered through celite. The organic layer was separated, washed twice with H_2O, dried over $MgSO_4$, and concentrated *in vacuo*. Column chromatography (1:1 EtOAc: hexanes) afforded compound **10** (1.021 g, 41% over 2 steps). IR (thin layer) 2927.1, 1695.2, 1511.5, 1081.6; ^{1}H NMR (500 MHz, $CDCl_3$) (E/Z carbamate isomers) δ 7.67 (s, 0.5H), 7.63 (s, 0.5H), 7.24 (m, 8H), 7.06 (dt, 1H, *J* = 1.5 Hz, *J* = 7.5 Hz), 6.97 (s, 0.5H), 6.83 (s, 0.5H), 5.10 (s, 2H), 5.08 (dd, 2H, *J* = 2.2 Hz, *J* = 10.6 Hz), 4.62 (bs, 1H), 3.63 (dd, 0.5H, *J* = 8.5 Hz, *J* = 10.5 Hz), 3.55 (dd, 0.5H, *J* = 8.5 Hz, *J* = 10.5 Hz), 3.49 (dd, 0.5H, *J* = 4.5 Hz, *J* = 10.0 Hz), 3.45 (dd, 0.5H, *J* = 4.5 Hz, *J* = 10.0 Hz), 3.33 (s, 1.5H), 3.32 (s, 3H), 3.29 (s, 1.5H), 2.91 (dd, 1H, *J* = 9.5 Hz, *J* = 15.0 Hz), 2.86 (s, 1.5H), 2.84 (s, 1.5H), 2.82 (dd, 1H, *J* = 8.0 Hz, *J* = 16.5 Hz); ^{13}C-NMR (500 MHz, $CDCl_3$) (E/Z carbamate isomers) δ 156.7, 156.6, 150.2, 138.8, 138.6, 137.1, 128.9, 128.8, 128.4, 127.8, 127.6, 125.6, 117.4, 116.9 116.3, 116.2, 95.2, 73.1, 72.8, 67.0, 66.8, 59.0, 56.4, 55.7, 30.2, 29.7, 28.5, 28.2; $[\alpha]^{23}_D = 2.8°$ (*c* = 0.5 in MeOH); HRMS calc'd for $C_{24}H_{30}N_3O_5$ [M+H], 440.21800, found 440.21582.



2-(*S*)-(methylamino)-3-{1-[2-(methoxymethoxy) phenyl]-imidazol-4-yl}-propyl methyl ether:

Compound **10** (250 mg, 0.57 mmol) was dissolved in EtOH (4.0 mL) and degassed. Pd/C 10% (250 mg) and cyclohexadiene (0.54 mL, 5.69 mmol) were added. The reaction was stirred under an inert atmosphere for 18 h and was then filtered through celite and concentrated to yield 2-(*S*)-(methylamino)-3-{1-[2-(methoxymethoxy) phenyl]-imidazol-

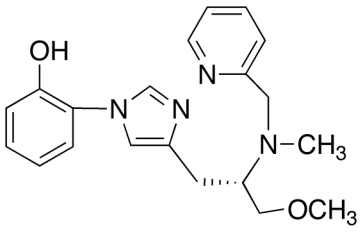
4(5)-yl}- propyl methyl ether (164 mg, 95%). IR (thin layer) 2935.3, 1511.8, 1081.4, 761.8; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.31 (m, 3H), 7.09 (dt, 1H, *J* = 1.4 Hz, *J* = 7.8 Hz), 7.02 (s, 1H), 5.17 (s, 2H), 3.52 (dd, 1H, *J* = 4.5 Hz, *J* = 9.6 Hz), 3.44 (dd, 1H *J* = 6.3 Hz, *J* = 9.6 Hz), 3.41 (s, 3H), 3.37 (s, 3H), 3.09 (m, 1H), 2.87 (dd, 1H, *J* = 6.2 Hz, *J* = 14.6 Hz), 2.79 (dd, 1H, *J* = 6.6 Hz, *J* = 14.6 Hz), 2.55 (s, 3H); ^{13}C-NMR (500 MHz, $CDCl_3$) δ 150.3, 139.0, 137.4, 128.9, 127.5, 125.6, 122.6, 117.8, 116.5, 95.2, 74.1, 59.3, 59.1, 56.5, 33.9, 29.3; $[\alpha]^{23}_D$= -6.5° (*c* = 0.7 in MeOH); HRMS calc'd for $C_{16}H_{24}N_3O_3$ [M+H], 306.18122, found 306.18347.



2-(*S*)-[(2-pyridylmethyl)methylamino]-3-{1-[2-(methoxymethoxy)phenyl]-imidazol-4-yl}-propyl methyl ether (11):

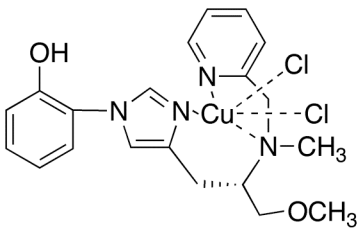
2-(*S*)-(Methylamino)-3-{1-[2-(methoxymethoxy) phenyl]-imidazol-4(5)-yl}- propyl methyl ether (1.160 g, 3.80 mmol) was dissolved in dichloroethane (31.6 mL), followed by the addition of pyridine-2-carboxaldehyde (0.37 mL, 3.80 mmol) and $Na(OAc)_3BH$ (1.127 g, 5.32 mmol). After 18 h under an inert atmosphere, a saturated $NaHCO_3$ aqueous solution (30 mL) was added to quench the reaction. The organic layer was separated and washed twice with H_2O, dried over $MgSO_4$, and concentrated *in vacuo* to afford compound **11** (1.501 g, >99%). IR (thin layer) 2927.8, 1511.6, 1119.7, 987.2, 757.3; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (ddd, 1H, *J* = 0.9 Hz, *J* = 1.7 Hz, *J* = 4.9 Hz), 7.63 (d, 1H, *J* = 1.3 Hz), 7.48 (dt, 1H, *J* = 1.4 Hz, *J* = 7.5 Hz), 7.36 (d, 1H, *J* = 7.8 Hz), 7.18 (m, 3H), 6.98 (m, 2H), 6.92 (d, 1H, *J* = 1.2 Hz), 5.05 (s, 2H), 3.85 (d, 1H, *J* = 14.6 Hz), 3.80 (d, 1H, *J* = 14.6 Hz), 3.51 (dd, 1H, *J* = 7.1 Hz, *J* = 10.0 Hz), 3.46 (dd, 1H, *J* = 4.0 Hz, *J* = 10.2 Hz), 3.27 (s, 3H), 3.24 (s, 3H), 3.23 (m, 1H), 2.85 (dd, 1H, *J* = 6.1 Hz, *J* = 14.5 Hz), 2.66 (dd, 1H, *J* = 8.1 Hz, *J* = 14.5 Hz), 2.29 (s, 3H); ^{13}C-NMR (500 MHz, $CDCl_3$) δ 160.8, 150.0, 148.6, 140.2, 136.7, 136.2, 128.5, 127.5, 125.3,

122.5, 122.3, 121.5, 117.2, 116.3, 95.0, 72.6, 62.9, 60.0, 58.7, 56.2, 38.0, 26.7; $[\alpha]^{23}_{D}$= -10.0° (*c* = 1.3 in MeOH); HRMS calc'd for $C_{22}H_{29}N_4O_3$ [M+H], 397.22342, found 397.22385.



2-(*S*)-[(2-pyridylmethyl)methylamino]-3-{1-(hydroxy)phenyl]-imidazol-4-yl}-propyl methyl ether (2):

Compound **11** (0.745 g, 1.88 mmol) was dissolved in CH_2Cl_2 (18 mL), followed by the bubbling of HCl gas (from H_2SO_4 and NH_4Cl) through the solution for 30 min. The solution was concentrated *in vacuo* to afford an off-white foam. The foam was washed with CH_2Cl_2, which was discarded. CH_2Cl_2 (~20 mL) was added to the foam and NaOH (aq. 50%) was added drop-wise with vigorous swirling until the foam dissolved into the organic layer. The organic layer was separated, dried over $MgSO_4$, and concentrated *in vacuo* to give ether ligand (**2**) (0.588 g, 89%) as an off-white oil. IR (thin film): 2925.8, 1712.1, 1463.6, 1116.3, 754.9; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (ddd, 1H, *J* = 0.9 Hz, *J* = 1.7 Hz, *J* = 5.0 Hz), 7.84 (d, 1H, *J* = 1.2 Hz), 7.57 (dt, 1H, *J* = 1.8 Hz, *J* = 7.7 Hz), 7.39 (d, 1H, *J* = 7.8 Hz), 7.17 (dd, 1H, *J* = 1.3 Hz, *J* = 7.8 Hz), 7.10 (m, 3H), 6.85 (ddd, 1H, *J* = 1.9 Hz, *J* = 6.9 Hz, *J* = 7.7 Hz), 3.86 (s, 2H), 3.52 (dd, 1H, *J* = 7.0 Hz, *J* = 10.1 Hz), 3.44 (dd, 1H, *J* = 4.2 Hz, *J* = 10.1 Hz), 3.25 (s, 3H), 2.86 (dd, 1H, *J* = 6.7 Hz, *J* = 14.6 Hz), 2.66 (dd, 1H, *J* = 7.2 Hz, *J* = 14.6 Hz), 2.33 (s, 3H); ^{13}C-NMR (500 MHz, $CDCl_3$) δ 160.7, 151.8, 139.4, 137.0, 136.8, 128.9, 125.5, 125.2, 123.2, 122.0, 119.5, 118.1, 117.7, 72.8, 62.6, 60.2, 58.9, 37.9, 26.7; $[\alpha]^{23}_{D}$= -5.6° (*c* = 1.1 in MeOH); HRMS calc'd for $C_{20}H_{25}N_4O_2$ [M+H], 353.19720, found 353.19752.

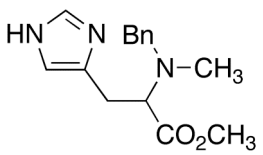


Cu-complex $[[Cu^{II}(L^{N3}OH)]_2(Cl_3)]^{\cdot}(ClO_4)$ (3):

Compound **2** (0.28 mmol, 100 mg) was dissolved in MeOH (2.8 mL). To this solution, dry $Cu(ClO_4)_2 \cdot 6\ H_2O$ (0.28 mmol, 105 mg) in MeOH (2.8 mL) was added drop-wise with stirring. Solid NaCl

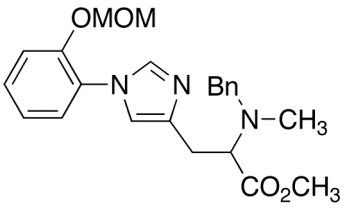
(0.85 mmol, 50 mg) was added in one portion. After gentle swirling for 30 seconds, the solution was filtered and the mother liquors were placed in a clean flask. Slow evaporation afforded X-ray quality crystals.

Melting point = 225-227 °C.



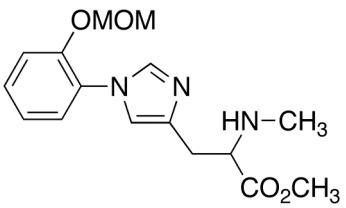
_N_-Benzyl-_N_-methyl-(_L_)-histidine methyl ester.[6]

H-(_L_)-His-OMe·2HCl (500 mg, 2.06 mmol) was dissolved in a minimum amount of methanol and neutralized with 10 mequiv (mmols exchange per mL resin) of Amberlite IRA-410 (OH form) using the batch technique. After gentle stirring for 5 min, the liquid phase was separated and concentrated to yield the neutral amine. The neutral amine was dissolved in MeOH (20.6 mL) and PhCHO (220 μL, 2.17 mmol) was added. After stirring for 1 h, $NaBH_3CN$ (143 mg, 2.17 mmol) was added. After stirring for 18 h, $(CH_2O)_n$ (194 mg, 2.06 mmol (for MW = 90.1)) was added. Upon complete dissolution of $(CH_2O)_n$ (approximately 5 h), $NaBH_3CN$ (143 mg, 2.17 mmol) was added and the reaction was allowed to proceed for 18 h. The reaction mixture was concentrated *in vacuo*, taken up in 10 mL of CH_2Cl_2 and washed twice with 5 mL of deionized water. Drying with anhydrous $MgSO_4$ and concentration *in vacuo* yielded *N*-benzyl-*N*-(*L*)-methyl-histidine methyl ester (554 mg, 99%) as a clear oil. IR (thin film) 3059.9, 2923.6, 1601.1, 1492.9, 1452.1 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.54 (d, 1H, J = 0.7 Hz), 7.33-7.24 (m, 5H), 6.81 (s, 1H), 3.79 (d, 1H, J = 11.0 Hz), 3.76 (s, 3H), 3.64 (d, 1H, J = 13.3 Hz), 3.62 (dd, 1H, J = 6.9 Hz, J = 7.9 Hz), 3.11 (dd, 1H, J = 6.8 Hz, J = 15.3 Hz), 2.99 (dd, 1H, J = 7.8 Hz, J = 15.5 Hz), 2.33 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 172.5, 138.8, 134.6, 129.1, 128.6, 127.5, 65.9, 59.3, 51.7, 48.3, 37.9, 25.8; $[\alpha]^{23}_D$ = -50.8° (c = 0.012 in MeOH); HRMS calc'd for $C_{15}H_{20}N_3O_2$ [M+H], 274.15500, found 274.15396.



Methyl 2-(*S*)-[(Benzyl)methylamino]-3-{1-[2-(methoxymethoxy)phenyl]-imidazol-4-yl}-propanoate.

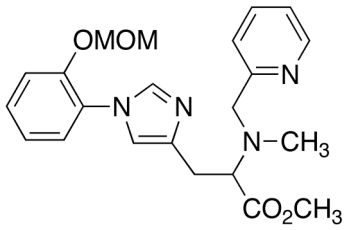
N-Benzyl-*N*-(*L*)-methyl-histidine methyl ester (108 mg , 0.41 mmol) was dissolved in 4.1 mL CH_2Cl_2. $Cu(OAc)_2$ (8 mg, 0.04 mmol) and 1-lead-triacetate-2-methoxymethoxy-benzene **9** (304 mg, 0.58 mmol) was added and the reaction mixture was allowed to stir under an inert atmosphere for 18 h. Approximately 4.1 mL of a saturated aqueous solution of Na_2S was added and the reaction mixture was allowed to stir for 15 minutes. The mixture was filtered through celite and the organic layer was washed with water, dried over $MgSO_4$, and concentrated *in vacuo.* Flash column chromatography of the resulting oil, eluting with EtOAc:Hex (1:1), then MeOH: EtOAc (1:9), afforded the desired coupled material (145 mg, 85%). IR (thin film) 2950.1, 1731.8, 1511.6, 1156.0, 736.9 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.72 (d, 1H, *J* = 1.3 Hz), 7.26 (m, 7H), 7.09 (ddd, 1H, *J* = 1.7 Hz, *J* = 7.0 Hz, *J* = 7.9 Hz), 6.98 (d, 1H, *J* = 1.3 Hz), 5.15 (s, 2H), 3.88 (dd, 1H, *J* = 6.7 Hz, *J* = 8.3 Hz), 3.81 (d, 1H, *J* = 13.6 Hz), 3.72 (s, 3H), 3.64 (d, 1H, *J* = 13.6 Hz), 3.38 (s, 3H), 3.20 (ddd, 1H, *J* = 0.4 Hz, *J* = 8.2 Hz, *J* = 14.6 Hz), 3.03 (ddd, 1H, *J* = 0.6 Hz, *J* = 6.7Hz, *J* = 14.6 Hz), 2.32 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 172.7, 163.4, 150.4, 139.7, 138.8, 137.2, 128.83, 128.3, 127.0, 125.7, 122.6, 117.7, 116.6, 95.3, 66.3, 58.9, 56.5, 51.2, 38.1, 28.9; $[\alpha]^{23}_D$ = -35.2 (*c* = 10.0 in MeOH); HRMS calc'd for $C_{23}H_{28}N_3O_4$ [M+H], 410.20743, found 410.20560.



Methyl 2-(*S*)-(methylamino)-3-{1-[2-(methoxymethoxy) phenyl]-imidazol-4-yl}-propanoate.

The product from the above reaction (1.176 g, 2.44 mmol) was dissolved in 5.1 mL of a MeOH:H_2O (6:1) solution and degassed thoroughly via the freeze/pump/thaw technique. Pd/C (10% Pd) was added and the flask was treated with 1 atm of

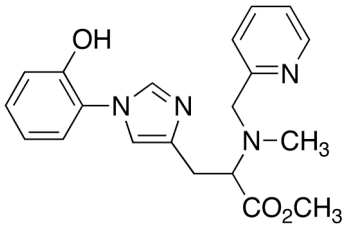
H_2 for 18 h. The reaction mixture was filtered through celite and concentrated to afford the desired secondary amine (762 mg, 98%). IR (thin film) 2952.0, 1732.6, 1512.5, 1155.6, 758.5 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.22 (m 3H), 7.01 (dt, 1H, *J* = 1.5 Hz, *J* = 7.3 Hz), 6.95 (s, 1H), 5.08 (s, 2H), 3.65 (s, 3H), 3.54 (t, 1H, *J* = 6.4 Hz), 3.32 (s, 3H), 2.98 (dd, 1H, *J* = 5.9 Hz, *J* = 14.5 Hz), 2.92 (dd, 1H, *J* = 6.9 Hz, *J* = 14.5 Hz), 2.35 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 174.7, 163.2, 150.0, 137.2, 128.7, 127.1, 125.3, 122.3, 117.7, 116.2, 94.7, 62.7, 56.1, 51.5, 34.3, 31.2; $[\alpha]^{23}_D$ = 4.0 (*c* = 21.2 in MeOH); HRMS calc'd for $C_{16}H_{22}N_3O_4$ [M+H], 320.16048, found 320.15740.



Methyl 2-(*S*)-[(2-pyridylmethyl)methylamino]-3-{1-[2-(methoxymethoxy)phenyl]-imidazol-4-yl}-propanoate.

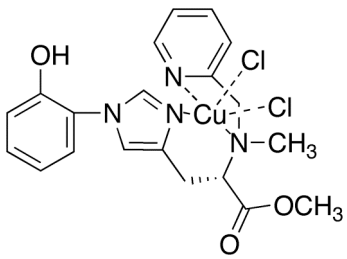
The secondary amine prepared above (2.376 g, 7.44 mmol) was dissolved in 62 mL of dichloroethane. 2-Pyridine carboxaldehyde (0.72 mL, 7.44 mmol) and $NaBH(OAc)_3$ (2.208 g, 10.41 mmol) were added and the mixture was allowed to react under an inert atmosphere for 18 h. The reaction mixture was quenched with approximately 62 mL of a concentrated aqueous solution of $NaHCO_3$. The organic layer was separated and washed with water, dried over $MgSO_4$, and concentrated *in vacuo*. Flash column chromatography of the resulting oil, eluting with EtOAc:Hex (1:1), then MeOH:EtOAc (1:9), afforded the MOM-protected ester ligand (2.476 g, 81%). IR (thin film) 2950.8, 1731.9, 1512.6, 1156.4, 758.4 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.45 (ddd, 1H, *J* = 0.9 Hz, *J* = 1.8 Hz, *J* = 4.9 Hz), 7.67 (d, 1H, *J* = 1.3 Hz), 7.54 (dt, 1H, *J* = 1.8 Hz, *J* = 7.7 Hz), 7.32 (d, 1H, *J* = 7.9 Hz), 7.23 (m, 3H), 7.05 (dddd, 2H, *J* = 1.5 Hz, *J* = 5.9 Hz, *J* = 7.9 Hz, *J* = 8.7 Hz), 6.97 (d, 1H, *J* = 1.2 Hz), 5.15 (s, 2H), 3.92 (d, 1H, *J* = 14.7 Hz), 3.87 (dd, 1H, *J* = 6.5 Hz, *J* = 8.5 Hz), 3.81 (d, 1H, *J* = 14.7 Hz), 3.18 (dd, 1H, *J* = 8.3 Hz, *J* = 14.5 Hz), 3.00 (dd, 1H, *J* = 6.5 Hz, *J* = 14.4

Hz), 2.37 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 172.4, 160.0, 150.2, 148.9, 138.6, 137.1, 135.4, 128.8, 127.5, 125.4, 122.6, 122.5, 121.9, 95.1, 66.6, 60.6, 56.3, 51.1, 38.4, 28.8; $[\alpha]^{23}_D$= -26.8 (*c* = 10.0 in MeOH); HRMS calc'd for $C_{22}H_{27}N_4O_4$ [M+H], 411.20268, found 411.20111.



Methyl 2-(*S*)-[(2-pyridylmethyl)methylamino]-3-{1-(hydroxy)phenyl]-imidazol-4-yl}-propanoate (4).

The MOM-protected ester ligand (324 mg, 0.72 mmol) was dissolved in 7.9 mL CH_2Cl_2. HCl gas was bubbled through the stirred solution for 30 min: the salt had crashed out of solution. The reaction mixture was concentrated to yield an off-white foam. Approximately 15 mL of CH_2Cl_2 was added to the flask followed by a minimum amount of 50% NaOH aqueous solution to effect solubility of the foam into the organic layer. The organic layer was separated, dried over $MgSO_4$, and concentrated *in vacuo* to yield ester ligand **4** (289 mg, 99%). IR (thin film) 2951.5, 1731.7, 1463.5, 1287.9, 753.5 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.41 (d, 1H, *J* = 4.3 Hz), 7.78 (s, 1H), 7.56 (dt, 1H, *J* = 1.3 Hz, *J* = 7.7 Hz), 7.27 (d, 1H, *J* = 7.7 Hz), 7.09, (m, 5H), 6.79 (t, 1H, *J* = 6.4 Hz), 3.89 (d, 1H, *J* = 14.6 Hz), 3.77 (d, 1H, *J* = 14.4 Hz), 3.66 (dd, 1H, *J* = 6.0 Hz, *J* = 18.4 Hz, 3.64 (s, 3H), 3.11 (dd, 1H, *J* = 7.5 Hz, *J* = 14.7 Hz), 2.98 (dd, 1H, *J* = 7.2 Hz, *J* = 14.6 Hz), 2.28 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 172.6, 163.4, 159.6, 148.8, 137.5, 137.2, 137.1, 128.9, 125.5, 125.1, 123.1, 122.2, 118.8, 118.4, 118.0, 66.3, 60.5, 51.4, 38.4, 29.1, 28.4; $[\alpha]^{23}_D$= -29.9 (*c* = 6.0 in MeOH); HRMS calc'd for $C_{20}H_{23}N_4O_3$ [M+H], 367.17647, found 367.17748.



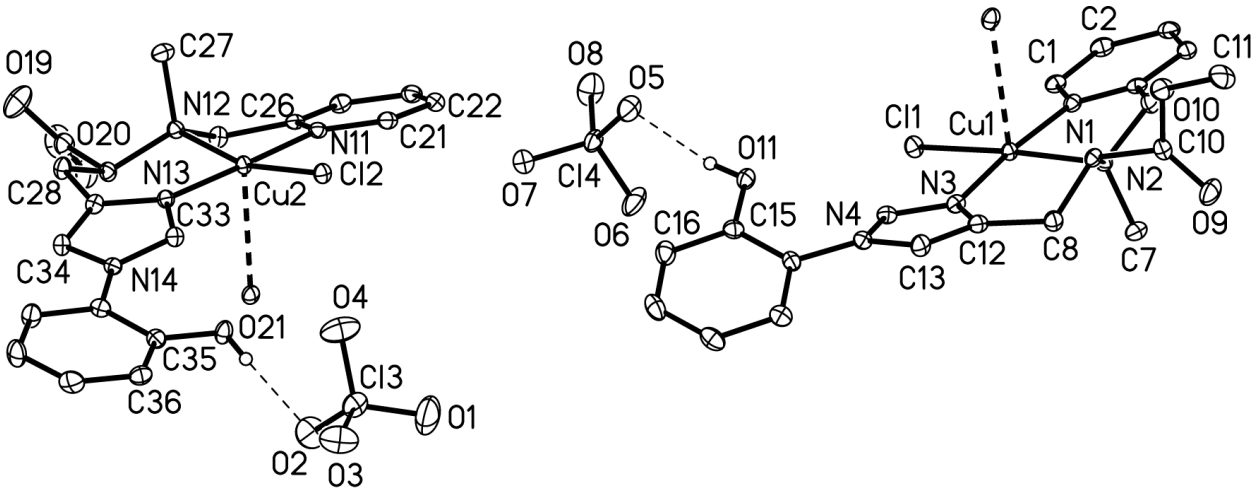
Cu-complex $\{[Cu^{II}(L^{N3}OH)]_2(Cl_3)\}^-(ClO_4)$ (5):

Tridentate ester ligand **4** (50 mg, 0.14 mmol) was dissolved in MeOH (0.68 mL). To this solution, $(CuClO_4)_2 \cdot 6\ H_2O$ (51 mg, 0.14 mmol) dissolved in MeOH (0.68 mL) was added drop-wise with

gentle stirring. A small amount of precipitate was observed upon complete addition. The sample was sonicated at rt for 5 min to dissolve the precipitate. Solid NaCl (20 mg, 0.3411 mmol) was added in one portion. After sitting for 10 minutes, the mother liquors were removed and filtered. Slow evaporation at rt open to air, afforded ortho-rhombic blue crystals (55 mg, 72%). Melting point: 229-230 °C.

Crystals of **5** were grown from a solution containing MeOH and NaCl. Crystal Data: $C_{20}H_{22}Cl_2CuN_4O_7$, M = 564.86, orthorhombic, a = 6.54660(10), b = 25.6151(5), c = 26.3379(6) Å, U = 4415.30(15) Å^3, T = 90(2) K, space group $P2_12_12_1$ (no. 19), Z = 8, μ(Mo-Kα) = 1.3 mm^{-1}, 58910 reflections measured, 10144 unique (R_{int} = 0.033) which were used in all calculations. The Flack parameter refined to -0.002(5). The final $wR(F^2)$ was 0.064 (all data). The crystal structure for **3** has been deposited at the Cambridge Crystallographic Data Center and allocated the reference no. 640796.

Crystal structure of **5** showing the two compounds in the asymmetric unit and the weakly coordinated axial chlorine atoms, Cu1…Cl' = 2.8591(5)Å, Cu2…Cl2" = 2.7340(5)Å . Thermal ellipsoids are drawn at the 50% probability level and hydrogen atoms are omitted for clarity except for the hydroxyl H atoms, which are retained in order to show the hydrogen bonding to perchlorate anions. Symmetry code: ' = x-1/2, 1/2-y, 1-z; " = ½+x, 3/2-y, 1-z.



Compound 5

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