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Chiral Tripodal Ligand Containing Three *N*-Heterocyclic Donor Functions and Its Copper Complexes: Crystallization of $[LCu^I]_2^{2+}$/$[L_2Cu^{II}]^{2+}$ Stereoisomers and Tyrosinase Activity

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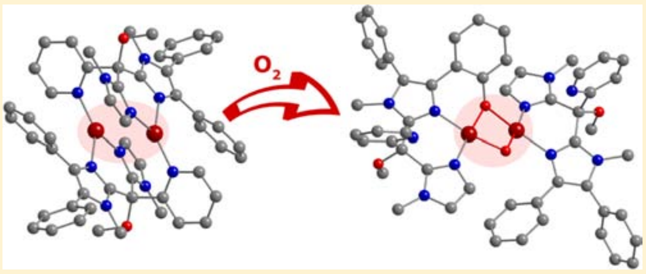
Supporting Information



ABSTRACT: A novel chiral ligand system **L** containing one pyridyl and two imidazolyl donor functions has been synthesized and investigated with respect to its Cu^I and Cu^{II} coordination chemistry. Reaction with $[Cu(MeCN)_4]PF_6$ and $[Cu(MeCN)_4]OTf$ led to the dimeric complexes $[LCu]_2X_2$ (**1**, X = PF_6; **2**, X = OTf) with the ligands **L** in different configurations (*R*,*S*). The ligand matrix formed in these complexes can also host a Cu^{II} ion instead of two Cu^I ions so that mixed crystals of $[L_2Cu]X_2$ and $[LCu]_2X_2$ can be produced. The pure compounds $[L_2Cu]X_2$ (**3**, X = PF_6; **4**, X = OTf) can be obtained by treatment of **1** and **2** with O_2 in acetonitrile, respectively. From the corresponding solution **3** crystallizes with the two **L** molecules in different configurations, while **4** crystallizes with the ligands in (*S*,*S*) or (*R*,*R*) configurations, respectively. Crystals containing the analogous diastereomers of **3** were obtained, besides those isolated previously, when this compound was synthesized by reaction of **1** with $AgPF_6$. On treating **2** with O_2 as the oxidant in acetonitrile, besides formation of **4**, additional evidence for oxygenation of **L** to L^{ox}, where one of the original phenyl units corresponds to a phenolate function, was found: The dinuclear complex $[L^{ox}Cu(OH)(OTf)CuL](OTf)$ (**5**) was isolated as the final product of O_2 activation and conversion, which resembles the one of tyrosinase. In acetonitrile **5** reacts further to give **4** and $[L^{ox}{}_2Cu_2](OTf)_2$ (**6**), and hence, product mixtures are obtained. In CH_2Cl_2 decomposition can be avoided, and hence, changing the solvent from acetonitrile to CH_2Cl_2 leads to selective formation of **5**.

INTRODUCTION

Histidine is one of the most abundant amino acids in the coordination spheres of metal ions belonging to nonheme metalloenzymes.[1−3] In proteins like carbonic anhydrase[2] or hemerythrin[3] even three histidine-based imidazole residues are binding to zinc and iron, respectively, and examples where this is the case in copper proteins include tyrosinase,[1,4] catecholoxidase,[5] and hemocyanin.[6] Consequently, a lot of research has been devoted in the last decades to the design and employment of multipodal ligands with *N*-heterocyclic donor functions for biomimetic chemistry. This has led, for instance, to the development of the pyrazole-based Tp (tris(pyrazolyl)borate)[7] ligands and also to tris(imidazolyl)methanes[8] featuring three imidazole units. In addition, pyridyl-based ligands are frequently employed in bioinorganic contexts, the most prominent example being the tetrapodal TPA (tris(pyridylmethyl)amine), where three pyridyl donors are linked to an amine.[9] The reaction pockets of metalloenzymes are intrinsically chiral, and this also translates to the first ligand sphere of the metal centers. Although certain protein functions do not utilize chirality in the immediate and remote surroundings of their metal centers directly during substrate conversion, in other cases, like cytochromes P450,[10] PAM,[11] tyrosinase,[1,4] or the lipoxygenases,[12] it allows for stereoselective reactions. We therefore contemplated the synthesis of chiral tripodal ligands that contain some of the donor functions approved in biomimetic or bioinspired chemistry, namely, imidazolyl, pyrazolyl, and pyridyl residues. Recently, we reported the synthesis of such a ligand and its employment in biomimetic iron chemistry.[13] Here we describe a further representative and considering the His_3 ligand spheres in various type 3 copper enzymes, like the ones mentioned above, its Cu^I and Cu^{II} coordination chemistry was investigated.

EXPERIMENTAL SECTION

General Procedures. All manipulations were carried out in a glovebox or else by means of Schlenk-type techniques involving the use of a dry argon atmosphere. ^1H and ^{13}C NMR spectra were recorded on a Bruker DPX 300 NMR spectrometer. ^1H NMR spectra were calibrated against the residual proton and ^{13}C NMR spectra against natural abundance ^{13}C resonances of the deuterated solvents. Microanalyses were performed on a HEKAtech Euro EA 3000 elemental analyzer. Infrared (IR) spectra were recorded using samples prepared as KBr pellets with a Shimadzu FTIR-8400S spectrometer.

Materials. Solvents were purified, dried, degassed, and stored over molecular sieves prior to use. $[Cu(MeCN)_4]PF_6$ and $[Cu(MeCN)_4]$-OTf were synthesized from Cu_2O and hexafluorophosphoric acid or

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trifluoromethanesulfonate acid in acetonitrile and recrystallized twice from acetonitrile/diethyl ether.

Synthesis of L. A 11.4 g (0.049 mol) amount of 1-methyl-4,5-diphenylimidazole dissolved in 30 mL of thf was treated with 19.4 mL (2.5 M in hexane, 0.049 mol) of *n*-BuLi at −78 °C. The mixture was stirred at this temperature for 30 min, and subsequently, a solution of 9.1 g (0.049 mol) of (1-methylimidazol-2-yl)(pyridine-2-yl)methanon (**I**) in 30 mL of thf was added. Overnight the mixture was warmed to room temperature and neutralized with 2.5 M sulfuric acid. The organic layer was separated and washed twice with H_2O. Aqueous layers were extracted twice with 10 mL of CH_2Cl_2, and all combined organic phases were dried over $MgSO_4$. Solvent was removed, and 12.6 g (0.030 mol, η = 61%) of the alcohol **II** was obtained as a yellow solid. This was dissolved in 30 mL of thf, and 1.36 g (0.057 mol, 1.9 equiv) of NaH was added carefully. After stirring for 7 days at room temperature the mixture was refluxed for 6 h. A 3.55 mL (0.057 mol, 1.9 equiv) amount of MeI was added, and after stirring for 3 h the solvent was removed in vacuo. A 30 mL amount of CH_2Cl_2 as well as 30 mL of H_2O were added and the layers separated. The aqueous layer was extracted twice with 20 mL of CH_2Cl_2, and all combined phases were dried over $MgSO_4$. Solvent was removed in vacuo, the yellow solid obtained was purified over a column of silica gel (ethylacetate: triethylamine = 9:1), and the solvent was removed at 45 °C in vacuo. A 1.53 g (3.513 mmol, η = 12% related to **II**) amount of **L** was obtained as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.20 (s, 3H, Ph-Im *NCH*$_3$), 3.53 (s, 3H, *OCH*$_3$), 3.62 (s, 3H, Im), 6.89 (d, 1H, $^3J_{H,H}$ = 0.8 Hz, Im **CH**-5), 7.02 (d, 1H, $^3J_{H,H}$ = 0.8 Hz, Im **CH**-4), 7.06 (d, 1H, $^3J_{H,H}$ = 7.2 Hz, Ph **CH**), 7.12 (t, 2H, $^3J_{H,H}$ = 7.2 Hz, Ph **CH**), 7.1 (d*t, 1H, Py **CH**-5), 7.32 (m, 2H, Ph **CH**), 7.41 (m, 5H, Ph **CH**), 7.69 (m, 1H, Py **CH**-4), 7.76 (d, 1H, $^3J_{H,H}$ = 8.0 Hz, Py **CH**-3), 8.53 (1H, d, $^3J_{H,H}$ = 4.4 Hz, Py **CH**-6). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 32.7 (Ph-Im *CH*$_3$), 35.0 (Im *CH*$_3$), 54.4 (*OCH*$_3$), 82.9 (**C**$_q$), 122.9 (Py **CH**-5), 123.4 (Im **CH**-5), 125.0 (Py **CH**-3), 126.0 (Ph **CH**), 126.7 (Im **CH**-4), 126.7 (Ph **CH**), 127.9 (Ph **CH**), 128.6 (Ph **CH**), 128.9 (Ph **CH**), 131.1 (Ph-Im Cq), 131.1 (Ph **CH**), 135.0 (Ph **C**$_q$), 135.9 (Ph **C**$_q$), 136.4 (Py **CH**-4), 145.4 (Ph-Im**C**$_q$-2), 146.1 (Im **C**$_q$-2), 147.5 (Py **CH**-6), 158.9 (Py **C**$_q$). IR (KBr): 3111 (w), 3054 (w), 2988 (w), 2947 (m), 2922 (m), 2824 (w), 1648 (w), 1601 (m), 1586 (m), 1568 (m), 1504 (m), 1465 (m), 1444 (m), 1430 (m), 1388 (w), 1320 (w), 1281 (m), 1253 (w), 1239 (w), 1150 (w), 1098 (m), 1078 (s), 1073 (s), 1057 (m), 1029 (m), 983 (m), 951 (w), 933 (w), 905 (w), 833 (w), 792 (m), 777 (s), 756 (m), 749 (m), 733 (m), 721 (m), 701 (s), 698 (s), 682 (m), 669 (m), 647 (w), 682 (m). ESI-MS (pos, MeCN): *m*/*z* = 436.2116 (calcd for $[LH]^+$ 436.2137).

Synthesis of $[LCu]_2(PF_6)_2$ (1). A 59 mg (0.135 mmol) amount of **L** was added to 50 mg (0.135 mmol) of $[Cu(MeCN)_4]PF_6$ in 4 mL of thf, and the reaction mixture was stirred overnight. The precipitate was separated by filtration and washed with 2 mL of thf as well as with 5 mL of diethyl ether. After drying 80 mg of **1** could be isolated in the form of a light yellow solid (0.062 mmol, η = 92%). Crystals suitable for single-crystal X-ray diffraction studies could be grown by layering an acetonitrile solution with diethyl ether, but due to the high sensitivity of **1** toward oxidants these contained 5% of cocrystallized **3**^{meso}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.24 (s, 3H, *OCH*$_3$), 3.29 (s, 3H, Ph-Im *NCH*$_3$), 3.55 (s, 3H, Im *NCH*$_3$), 7.00 (s, 1H, Im **CH**-5), 7.08 (s, 1H, Im **CH**-4), 7.22−7.42 (m, 11H, Ph **CH** and Py **CH**-5), 7.90 (m, 2H, Py **CH**-3/4), 8.53 (1H, d, $^3J_{H,H}$ = 2.8 Hz, Py **CH**-6). IR (KBr): 3151 (w), 3132 (w), 2965 (m), 2914 (w), 1603 (m), 1535 (w), 1492 (m), 1474 (m), 1442 (w), 1427 (w), 1380 (w), 1369 (m), 1287 (w), 1247 (m), 1216 (w), 1128 (w), 1107 (m), 1073 (m), 1060 (m), 1048 (m), 978 (w), 909 (w), 875 (m), 839 (vs), 808 (m), 767 (m), 751 (w), 710 (w), 557 (s). ESI-MS (pos, MeCN): *m*/*z* = 1024.2766 (calcd for $[L_2Cu_2CN]^+$ 1024.2741). Anal. Calcd for $C_{54}H_{50}Cu_2F_{12}N_{10}O_2P_2$ (1288.06 g/mol): C, 50.35; H, 3.91; N, 10.87. Found: C, 50.83; H, 3.97; N, 10.55.

Synthesis of $[LCu]_2(OTf)_2$ (2). Treatment of 50 mg (0.115 mmol) of **L** with 43 mg (0.115 mmol) of $[Cu(MeCN)_4]OTf$ dissolved in 2 mL of thf led to instantaneous precipitation of a light yellow solid. This was isolated by filtration and washed once with 2 mL of thf as well as with 2 mL of diethyl ether. After drying 66 mg (0.051 mmol, η = 89%) of **2** was isolated. Crystals suitable for single-crystal X-ray diffraction studies could be obtained by layering an acetonitrile solution of **1** with diethyl ether. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.26 (s, 3H, *OCH*$_3$), 3.28 (s, 3H, Ph-Im *NCH*$_3$), 3.54 (s, 3H, Im *NCH*$_3$), 6.99 (s, 1H, Im *CH-5*), 7.07 (d, 1H, $^3J_{H,H}$ = 0.8 Hz, Im **CH**-4), 7.22−7.27 (m, 5H, Ph **CH**), 7.33 (q, 1H, $^3J_{H,H}$ = 4.4 Hz, Py **CH**-5), 7.37−7.43 (m, 5H, Ph **CH**), 7.88 (d, 2H, $^3J_{H,H}$ = 4.4 Hz, Py **CH**-3/4), 8.53 (1H, d, $^3J_{H,H}$ = 4.8 Hz, Py **CH**-6). ^{13}C NMR ($CDCl_3$): δ = 33.1 (*OCH*$_3$), 35.2 (Ph-Im *NCH*$_3$), 52.8 (Im *NCH*$_3$), 80.2 (**C**$_q$*OCH*$_3$), 119.6 (Ph **CH**), 121.4 (Py **CH**-3), 122.8 (Ph **CH**), 123.6 (Py **CH**-5), 124.9 (Im **CH**-5), 126.6 (Im **CH**-4), 127.5 (Ph **CH**), 127.7 (2C, Ph **CH**), 128.7 (2C, Ph **CH**), 129.1 (Ph **CH**), 129.3 (2C, Ph **CH**), 131.1 (2C, Ph **CH**), 132.3 (Ph-Im **C**$_q$-5), 133.2 (Ph-Im **C**$_q$-4), 136.7 (Ph-Im **C**$_q$*CH*), 137.2 (Py **CH**-4), 143.7 (2C, Im **C**$_q$-2, Ph-Im **C**$_q$-2), 149.7 (Py *CH-6*). IR (KBr): 3119 (w), 3058 (w), 2957 (m), 2934 (w), 1599(m), 1535 (w), 1490 (m), 1472 (m), 1457 (m), 1443 (m), 1267 (vs), 1223 (m), 1151 (w), 1111 (w), 1075 (m), 1057 (w), 1030 (s), 990 (m), 915 (w), 776 (m), 770 (m), 756 (m), 705 (w), 636 (s), 573 (w), 517 (m). ESI-MS (pos, MeCN): *m*/*z* = 1024.2736 (calcd for $[L_2Cu_2CN]^+$ 1024.2741). Anal. Calcd for $C_{56}H_{50}Cu_2F_6N_{10}O_8S_2$ (1296.27 g/mol): C, 51.89; H, 3.89; N, 10.81; S, 4.95. Found: C, 52.18; H, 3.86; N, 10.81; S, 5.00.

Synthesis of $[L_2Cu](PF_6)_2$ (3). Method a: 120 mg (0.093 mmol) of **1** was dissolved in acetonitrile, and the argon atmosphere in the Schlenk tube was exchanged by O_2. Within 3 min the reaction mixture turned green, and after stirring overnight it was layered with diethyl ether. **3**^{meso} (92 mg, 0.075 mmol, η = 80%) could be obtained in the form of bright green crystals, which were suitable for single-crystal X-ray diffraction studies. In addition to these crystals, 18 mg of a light green solid could be obtained which could not be identified unambiguously but possibly belongs to a copper complex with the oxygenated ligand **L**^{ox}. Method b: After dissolution of 10 mg (0.015 mmol) of **1** and 6.7 mg (0.015 mmol) of **L** in 1 mL of acetonitrile and treatment with 3.9 mg (0.015 mmol) of $AgPF_6$ the solution immediately turned green and elemental silver precipitated. After filtration the solution was layered with diethyl ether, resulting in formation of bright green (**3**^{meso}) and grass green (**3**^{rac}) crystals (together 17 mg, 0.014 mmol, η = 93%) which were suitable for X-ray diffraction studies. IR (KBr), **3**^{meso}: 3168 (w), 3147 (w), 3062 (w), 2959 (w), 1603 (m), 1591 (m), 1535 (w), 1497 (m), 1463 (m), 1445 (m), 1437 (m), 1399 (w), 1268 (w), 1178 (w), 1112 (m), 1085 (m), 1053 (m), 1026 (m), 994 (m), 916 (w), 897 (w), 877 (m), 839 (vs), 787 (m), 772 (s), 757 (w), 712 (w), 701 (m), 667 (w), 558 (s). IR (KBr), **3**^{rac}: 3148 (w), 3050 (w), 3000 (w), 2964 (w), 2837 (w), 1585 (m), 1574 (w), 1505 (m), 1497 (m), 1457 (m), 1445 (m), 1436 (m), 1399 (w), 1321 (w), 1285 (w), 1225(w), 1184 (w), 1164 (w), 1131 (w), 1108 (m), 1081 (m), 1056 (w), 1025 (w), 1005 (m), 993(m), 921 (w), 897 (w), 877 (m), 837 (vs), 798 (m), 776 (s), 755 (m), 734 (w), 705 (m), 698 (m), 663 (w), 557 (s). Anal. Calcd for $C_{54}H_{50}CuF_{12}N_{10}O_2P_2$ (1224.51 g/mol): C, 52.97; H, 4.12; N, 11.44. Found: C, 53.01; H, 4.06; N, 11.69.

Synthesis of $[L_2Cu](OTf)_2$ (4). Method a: 12 mg (0.032 mmol) of **2** was dissolved in acetonitrile, and the argon atmosphere in the Schlenk tube was exchanged by O_2. Within 3 min the reaction mixture turned green, and after stirring overnight it was layered with diethyl ether. A 9 mg (0.007 mmol, η = 49%) amount of **4**^{rac} could be obtained in the form of grass green crystals, which were suitable for single-crystal X-ray diffraction studies. Method b: 10 mg (0.015 mmol) of **2** and 6.7 mg (0.015 mmol) of **L** were dissolved in 1 mL of acetonitrile and treated with 4.2 mg (0.015 mmol) of AgOTf. The solution immediately turned green along with precipitation of elemental silver. After filtration the green solution was layered with diethyl ether, which led to formation of 16 mg (0.013 mmol, η = 84%) **4**^{rac} in the form of grass green crystals. Method c: 20 mg of **L** (0.046 mmol) and 8.3 mg (0.023 mmol) $Cu(OTf)_2$ were dissolved in acetonitrile. After layering the resulting green solution with diethyl ether grass green crystals of **4**^{rac} (26 mg, 0.021 mmol, η = 92%) could be obtained. IR (KBr) **4**^{rac}: 3148 (w), 3050 (w), 3000 (w), 2964 (w), 2837 (w), 1585 (m), 1574 (w), 1505 (m), 1497 (m), 1457 (m), 1445 (m), 1436 (m), 1399 (w), 1321 (w), 1285 (w), 1225(w), 1184 (w), 1164 (w), 1131 (w), 1108 (m), 1081 (m), 1056 (w), 1025 (w), 1005 (m), 993(m), 921 (w), 897 (w), 877 (m), 837 (vs), 798 (m), 776 (s), 755 (m), 734 (w), 705 (m), 698 (m), 663 (w), 557 (s). ESI-MS (pos, MeCN): *m*/*z* = 959.3544 (calcd for $[L_2CuCN]^+$ 959.3439; 1082.2923 (calcd for $[L_2CuOTf]^+$). Anal. Calcd for $C_{56}H_{50}CuF_6N_{10}O_8S_2$ (1232.72 g/mol): C, 54.56; H, 4.09; N, 11.36; S, 5.20. Found: C, 54.10; H, 3.97; N, 11.60; S, 5.12.

Synthesis of a Solid Solution of 2 and 4^{meso}. A 0.7 mg (0.0005 mmol) amount of **2** and 6 mg (0.0049 mmol) of **4** were dissolved in acetonitrile and layered with diethyl ether. Among grass green crystals of 4^{rac} yellow green crystals of a solid solution of **2** and 4^{meso} were formed. The ratio of **2** and 4^{meso} in the crystal measured by single-crystal X-ray diffraction was 34:66 (see Supporting Information).

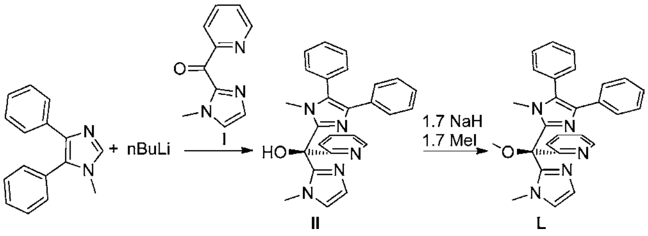
Synthesis of $[LCu(OH)(OTf)CuL^{ox}](OTf)$ (5). Method a: 15 mg (0.0116 mmol) of **2** was suspended in 0.5 mL of dichloromethane, and the argon atmosphere in the Schlenk tube was exchanged by O_2. Overnight the reaction mixture turned brown. Subsequently, it was layered with diethyl ether at −30 °C, which lead to precipitation of 13.5 mg (0.0102 mmol, η = 88%) of **5** in form of a brown powder. Method b: 109 mg (0.084 mmol) of **2** was dissolved in 2 mL of acetonitrile, and the argon atmosphere in the Schlenk tube was exchanged by O_2. Within 10 min the reaction mixture turned green, and after stirring for another hour it was layered with diethyl ether. From such solutions crystals of **5** and 4^{rac} grew at room temperature, which were separated mechanically. Brown crystals of **5** were suitable for single-crystal X-ray diffraction studies. IR (KBr) **5**: 3607 (m), 3124 (w), 3058 (w), 2972 (w), 2939 (w), 2843 (w), 1601 (w), 1585 (m), 1506 (m), 1470 (m), 1461 (m), 1384 (w), 1272 (vs), 1266 (vs), 1243 (s), 1224 (m), 1149 (s), 1108 (m), 1079 (m), 1056 (w), 1030 (vs), 1003 (m), 993 (m), 920 (w), 858 (w), 792 (m), 778 (m), 753 (m), 733 (w), 715 (m), 707 (m), 668 (w), 637 (vs), 619 (w), 572 (w), 517 (m). ESI-MS (pos, MeCN): *m*/*z* = 498.1363 (calcd for $[LCu]^+$ 498.1455); 513.1223 (calcd for $[L^{ox}Cu]^+$ 513.1326); 948.3281 (calcd for $[LL^{ox}Cu]^+$ 948.3385). Anal. Calcd for $C_{56}H_{50}Cu_2F_6N_{10}O_{10}S_2$ (1328.27 g/mol): C, 50.64; H, 3.79; N, 10.55; S, 4.83. Found: C, 50.30; H, 3.78; N, 10.76; S, 4.87.

Synthesis of $[(L^{ox})_2Cu_2](OTf)_2$ (6). **6** is formed by reaction of **2** and O_2 in acetonitrile as described in the discussion. It also forms if acetone is used as the solvent for this reaction, and in contrast to acetonitrile this allows a more facile separation of **6** from the other products because it is not soluble. Therefore, we only report here the synthesis in acetone. A 19 mg (0.0147 mmol) amount of **2** was suspended in 0.5 mL of acetone, and the argon atmosphere in the Schlenk tube was exchanged by O_2. Overnight the reaction mixture turned brown, and it was stirred for another 4 days. This led to precipitation of **6** as a green powder, which was filtered off and dried in vacuum. A 7 mg (0.0053 mmol, η = 36%) amount of **6** could be obtained. Crystals suitable for X-ray diffraction studies could be obtained by layering a solution of **6** in acetonitrile with diethyl ether. IR (KBr) **6**: 3450 (m), 3136 (w), 3058 (w), 3048 (w), 2959 (w), 2942 (w), 2835 (w), 1599 (w), 1586 (m), 1507 (m), 1465 (m), 1448 (m), 1437 (m), 1407 (w), 1284 (s), 1267 (s), 1236 (vs), 1179 (m), 1163 (s), 1137 (m), 1107 (m), 1075 (m), 1051 (w), 1027 (s), 1004 (m), 994 (m), 924 (w), 846 (m), 792 (m), 788 (m), 775 (m), 759 (m), 732 (w), 709 (m), 668 (w), 638 (vs), 619 (w), 585 (w), 572 (w), 518 (m). ESI-MS (pos, MeCN): *m*/*z* = 513.1230 (calcd for $[L^{ox}Cu]^+$ 513.1326); 933.3323 (calcd for $[(L^{ox})_2Cu]^+$ 933.3514); 1054.2454 (calcd for $[(L^{ox})_2Cu_2CN]^+$ 1054.2465). Anal. Calcd for $C_{56}H_{48}Cu_2F_6N_{10}O_{10}S_2$ (1322.25 g/mol): C, 50.71; H, 3.65; N, 10.56; S, 4.84. Found: C, 51.00; H, 3.67; N, 10.70; S, 4.94.

■ RESULTS AND DISCUSSION

Ligand Synthesis. Ligand synthesis started from a ketone **I** (see Scheme 1) that had been prepared before by Canty et al.[14] and contains a pyridyl as well as an imidazolyl moiety already. Reaction of **I** with deprotonated 2,3-diphenyl-1-methylimidazole yielded in the alcohol **II**. As the alcohol function was anticipated to disturb coordination via the three *N*-donor functions, **II** was further reacted with NaH and MeI in order to methylate this acidic function. This finally gave the potential ligand **L** containing three different *N*-donor functions connected to a methoxymethine unit. The central carbon atom in **L** is thus chiral, and the compound is obtained in the form of a racemic mixture, which was employed without prior separation into the pure enantiomers. Nevertheless, chirality was found to have interesting implications on complex formation and crystallization.

Scheme 1. Synthesis of Ligand L



Complex Synthesis. Treatment of **L** with $[Cu(MeCN)_4]$-PF_6 led to a product which proved very sensitive to air and was identified as $[LCu]_2(PF_6)_2$ (**1**) by elemental analysis, mass spectrometry, and NMR spectroscopy (see eq 1). Analogously, reaction with $[Cu(MeCN)_4]OTf$ led to $[LCu]_2(OTf)_2$ (**2**).

$$2L + 2[Cu(MeCN)_4]X \rightarrow [LCu]_2(X)_2$$
$$(X = PF_6(\mathbf{1}), OTf(\mathbf{2})) \tag{1}$$

Crystals of **2** suitable for single-crystal X-ray diffraction could be grown by carefully adding a diethyl ether phase on top of a saturated solution of **2** in acetonitrile, and the result of a corresponding analysis is shown in Figure 1. The complex crystallizes as a dimer: The two imidazole-based arms of **L** coordinate to one copper(I) center, while the pyridyl donor function binds to a second LCu^I entity, whose pyridyl unit forms a bridge to the first one. Within one molecule one of the ligands has an (*R*) configuration, the other one possesses an (*S*) configuration.

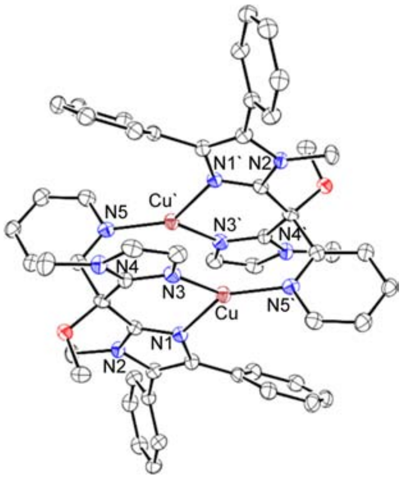


Figure 1. Molecular structure of the cation $[LCu]_2^{2+}$ of **2**. Hydrogen atoms are omitted for clarity. Selected bond lengths [Angstroms] and angles [degrees]: N1−Cu 2.000(3), N3−Cu 1.976(3), N5−Cu 1.942(3), Cu−Cu 2.8653(9); N1−Cu−N3 92.32(11), N1−Cu−N5 137.83(11), N3−Cu−N5 127.89(11).

Complex **2** crystallizes in the centrosymmetric space group *P*-1 with the inversion center located directly between the two

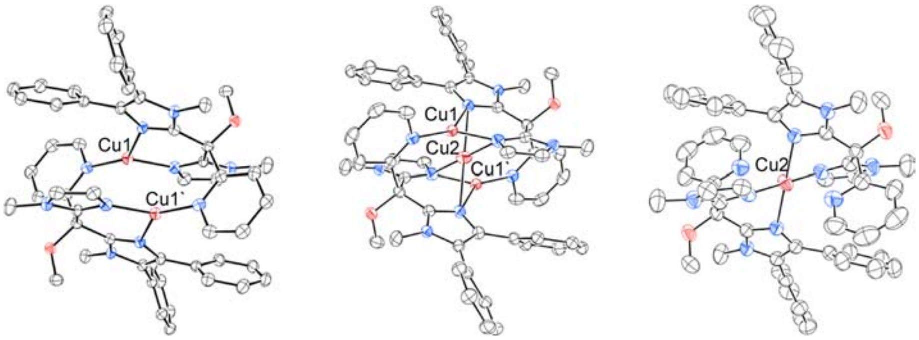


Figure 2. Molecular structures of the cation $[\mathrm{LCu}]_2^{2+}$ within **2** (a), solid solution of $[\mathrm{LCu}]_2^{2+}$ and $[\mathrm{L_2Cu}]^{2+}$ with $\mathrm{PF_6^-}$ counterions (b), and $[\mathrm{L_2Cu}]^{2+}$ within **3** (c). Hydrogen atoms are omitted for clarity.

copper ions. Due to the inversion center between both metal ions the complex possesses the ligand in both configurations. Each copper center is coordinated by three nitrogen atoms in a trigonal planar fashion. The angles at the copper atoms vary between 92.32° (N1−Cu−N3) and 137.83° (N1−Cu−N5), indicating a strongly distorted coordination sphere. The $\mathrm{Cu{-}N_{pyridyl}}$ bond (Cu−N5 1.942(3) Å) is slightly shorter than the $\mathrm{Cu{-}N_{imidazolyl}}$ (Cu−N3 1.976(3) Å) and the $\mathrm{Cu{-}N_{(phenyl)imidazolyl}}$ bonds (Cu−N1 2.000(3) Å).

Dosy NMR experiments indicate that complex **2** in solution exists maily in its monomeric form (ca. 90%); only 10% remains dimeric (see Supporting Information).

An interesting phenomenon could be observed: for complex syntheses starting materials were employed that were not completely free of copper(II) impurities (readily formed in contact with air). In this case the $[\mathrm{LCu}]_2(\mathrm{X})_2$ products cocrystallized with $[\mathrm{L_2Cu}]\mathrm{X_2}$ (X = $\mathrm{PF_6}$ (**3**), OTf (**4**)) in the form of a solid solution (ratio 95: 5). This becomes possible as the ligand matrix, as depicted in Figure 1, without significant rearrangement can also bind a copper(II) ion in its center instead of two copper(I) ions in the periphery as shown in Figure 2 for the case of X = $\mathrm{PF_6}$. The copper(II) ion is bound in a square planar fashion by four imidazole units of the two ligand molecules. The remaining two donor functions from the pyridyl residues seem to complete an octahedral coordination sphere, but a Cu−N distance of 2.8486(34) Å indicates, if at all, only very weak bonds. By comparison, the bond distances between the imidazole-based nitrogen atoms and the copper ion (Cu−N2 2.004(3) Å, Cu−N3 2.320(3) Å) are in the typical range for coordinative Cu−N bonds. Therefore, the coordination sphere basically has to be regarded as square planar.

Complex Oxidation. In the solid state complexes **1** and **2** contain two $\mathrm{Cu^I}$ centers, which are bound by three N-heterocyclic donor functions, each with a Cu···Cu distance of 2.8 Å, and this situation resembles the one of dicopper enzymes like tyrosinase, catecholoxidase, or hemocyanine, although the Cu···Cu separation in the enzymes is somewhat larger. As these enzymes readily react with $\mathrm{O_2}$ to give $\mathrm{Cu^{II}}_2$−peroxido moieties, we tested the $\mathrm{O_2}$ reactivity of **1** and **2** in the next step. Reacting **1** dissolved in acetonitrile with $\mathrm{O_2}$ the colorless solution gradually turned green, and layering of the resulting solution with diethyl ether yielded bright green crystals, the analysis of which proved exclusive formation of **3**. Accordingly, X-ray analysis provided the molecular structure of pure **3**, as it had been deduced already as part of the solid solution obtained as described above. While the observations made in the course of the reaction of **2** with $\mathrm{O_2}$ were basically the same, the crystals obtained of the resulting product **4** differed in color from those obtained of **3**. Instead of bright green they were grass green, and X-ray analysis gave a surprise: Indeed, a complex with the composition $[\mathrm{L_2Cu}]\mathrm{X_2}$ had been formed, too, but unlike in the case of **3** the ligands **L** within the complex cation $[\mathrm{L_2Cu}]^{2+}$ contained identical configurations (both the (*S*,*S*) and the (*R*,*R*) combinations were found in the crystal). This is due to the fact that **4** crystallizes in the acentric space group *Cc* with the complex molecule lying on a general position. The opposite enantiomer in the unit cell is generated due to the C-glide plane. Copper centers are coordinated distorted tetrahedrally (see Figures 3 and 4); the corresponding diastereomers will be

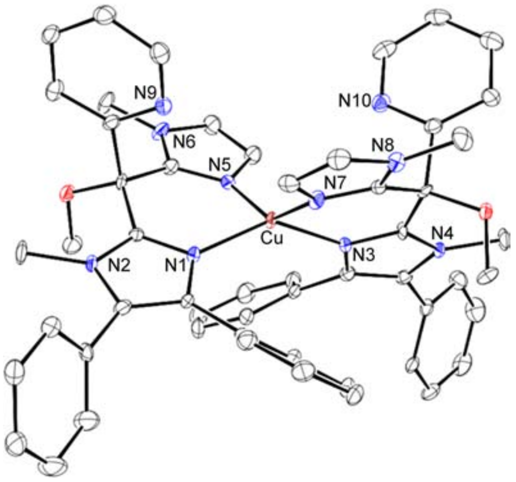


Figure 3. Molecular structure of the cation $[\mathrm{L_2Cu}]^{2+}$ of $\mathbf{4}^{\mathrm{rac}}$. Hydrogen atoms are omitted for clarity. Selected bond lengths [Angstroms] and angles [degrees]: N1−Cu 1.972(2), N3−Cu 1.9760(19), N5−Cu 1.941(2), N7−Cu 1.9269(19); N1−Cu−N3 141.67(8), N1−Cu−N5 93.28(8), N1−Cu−N7 98.89(8), N3−Cu−N5 100.45(8), N3−Cu−N7 92.49(8), N5−Cu−N7 141.16(8).

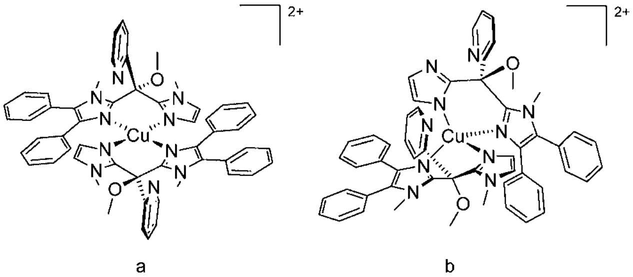


Figure 4. Illustration of the two possible structures of the cation $[\mathrm{L_2Cu}]^{2+}$: (a) the "meso" form and (b) the "rac" form ((*R*,*R*) shown).

distinguished throughout the rest of the discussion by the superscript “rac”, while the (*S*,*R*) configuration will be designated with “meso”.

Again the two ligand molecules coordinate in a bidentate fashion via the imidazole-based nitrogen atoms, while the pyridyl units remain pending. The angles at the copper center vary between 92.68(12)° and 141.86(11)°.

Thus, setting out from almost identical starting situations in **1** and **2** that only differ in the weakly coordinating counteranions and possess meso configurations reaction with O_2 leads to $\mathbf{3}^{\mathbf{meso}}$ in the case of **1** and to $\mathbf{4}^{\mathbf{rac}}$ in the case of **2**. Obviously, the anions play a decisive role, although they do not interact significantly with complex cations of either **1** and **2** or products **3** and **4**. To examine whether they exert their influence in cooperation with O_2 or its reduced species formed in the course of the oxidation reaction, an alternative synthetic route was tested using $AgPF_6$ and AgOTf as single-electron oxidants, respectively: 2 equiv of those were reacted with $[LCu]_2X_2$ dissolved in acetonitrile in the presence of an additional equivalent of **L**. As expected, this led to precipitation of silver and clean, almost quantitative formation of **3** and **4**, respectively. Again, the resulting solutions were layered with diethyl ether to crystallize the products. While crystallization of **4** again led to grass green crystals of $\mathbf{4}^{\mathbf{rac}}$, a mixture of bright green and grass green crystals (ratio 4:1) was obtained in the case of **3**. As anticipated, the bright green crystals turned out to be crystals of $\mathbf{3}^{\mathbf{meso}}$, while the grass green crystals, as already expected based on the color, corresponded to $\mathbf{3}^{\mathbf{rac}}$, which was confirmed by means of X-ray analysis (see Supporting Information). If such crystals of $\mathbf{3}^{\mathbf{rac}}$ were added to the solution of **3** during the crystallization process as seeds, **3** crystallized in the form of $\mathbf{3}^{\mathbf{rac}}$ even quantitatively. However, if these crystals of $\mathbf{3}^{\mathbf{rac}}$ were then recrystallized in the absence of seeds, $\mathbf{3}^{\mathbf{meso}}$ was isolated almost exclusively. This shows that there must be an equilibrium in solution containing $[LCu]^{2+}$, free **L**, $\mathbf{3}^{\mathbf{meso}}$, and $\mathbf{3}^{\mathbf{rac}}$, and obviously from this mixture $\mathbf{3}^{\mathbf{meso}}$ crystallizes first either because it is the major, thermodynamically most stable species or because it crystallizes best. In the case of **4** obviously $\mathbf{4}^{\mathbf{rac}}$ is favored.

To test whether ligand exchange is fast on the NMR time scale, **L** was added to solutions of **3** and **4** in d_3-acetonitrile, and a ^1H NMR spectrum was recorded. Sharp signals observed for **L** beside the very broad paramagnetically shifted signals of **3** or **4** indicated that the equilibrium was slow on the NMR time scale, Figure 5.

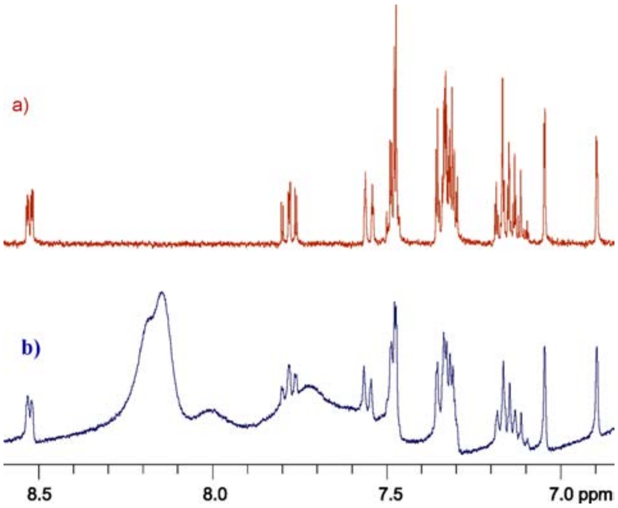


Figure 5. NMR spectra of (a) **L** and (b) **3** + **L** (molecular ratio 4:1) in d_3-MeCN.

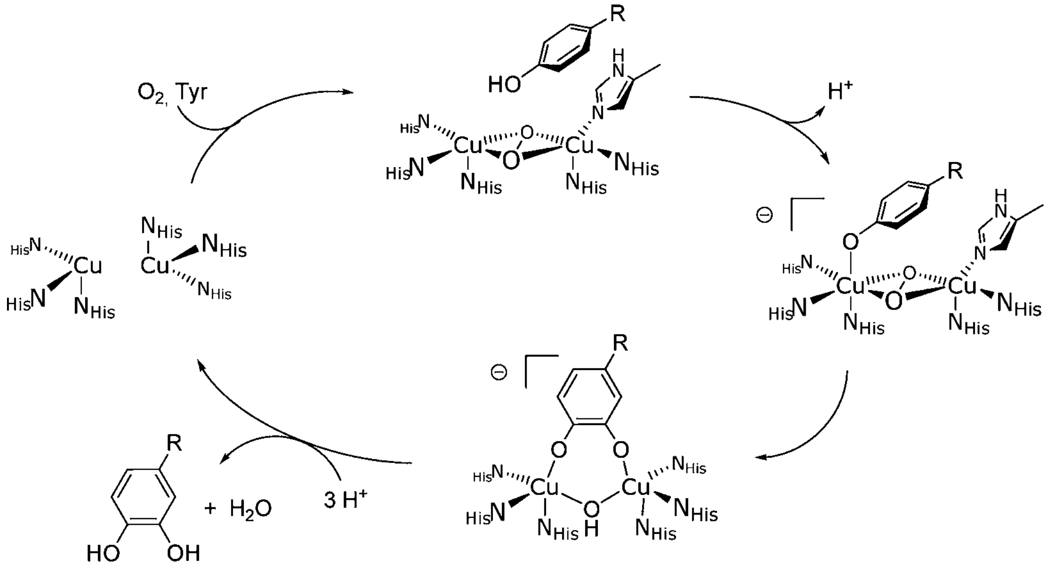
Unlike **3**, **4** crystallized only in the form of one diastereomer, although a variety of synthetic and crystallization routes were tested: For instance, **4** was not only synthesized by the methods mentioned before but also by reacting 2 equiv of **L** with $Cu(OTf)_2$, and crystallization was performed at various temperatures, in different solvents like CH_2Cl_2 or acetone, as well as by evaporation of the solvent from saturated solutions of **4**. Independent of these variations, pure **4** always crystallized, if at all, as $\mathbf{4}^{\mathbf{rac}}$ though. $\mathbf{4}^{\mathbf{meso}}$ could only be obtained in the form of solid solutions with **2**, but such solid solutions are only stable up to a Cu^{II} ratio of 66%. If this Cu^{II} ratio is exceeded, $\mathbf{4}^{\mathbf{rac}}$ is formed.

Tyrosinase Activity. With the background described above a lot of bioinorganic chemistry[15] has been reported in the past, setting out with Cu^I in N donor ligand environments for simulation of the histidine-rich coordination spheres often found in copper-based oxygenases/oxidases. Subsequent treatment with O_2 then often led to functional systems that oxidized the ligands or even external substrates in a biomimetic fashion.[15] Some of these systems[16] modeled the function of tyrosinase, which promotes ortho-hydroxylation of tyrosine via a mechanism shown in a simplified way in Scheme 2.

Investigating the reactions of **1** or **2** with O_2 in acetonitrile leading to **3** or **4**, respectively, formation of byproducts was observed, and in the case of **2**, it proved possible to adjust the experimental conditions such that these became the major products, so that an adequate characterization could be performed. Even crystalline material could be obtained, and single-crystal X-ray analysis identified the product as $[L^{ox}Cu(OH)(OTf)CuL](OTf)$ (**5**) (Figure 6). In contrast to **2**, which is an oxidation product, **5** is the product of an *oxygenation*: compared to **2** it contains two additional O atoms, which are part of the hydroxide and alkoxide ligands, Figure 6. Since in the ESI mass spectrum a signal for the cationic fragment $[L^{ox}Cu]^+$ could be detected, it could be shown that the O atom of the alkoxide ligand originates from O_2: When the reaction was performed with $^{18}O_2$ instead of $^{16}O_2$ a shift by two mass units was observed for this signal (m/z = 513.12 with ^{16}O and 515.12 with ^{18}O). Unfortunately, a complex cation containing the Cu(OH)Cu unit, for example, $[L^{ox}Cu(OH)(OTf)CuL]^+$, could not be detected by mass spectroscopy, so that we only can assume that the O atom of the hydroxide ligand comes from O_2, too, which is reasonable. In this case, after activation O_2 has exploited its four oxidation equivalents to oxidize the two Cu^I centers to the oxidation state +II and oxygenate the C−H bond of a phenyl residue of **L** to give the aryloxide ligand $\mathbf{L}^{\mathbf{ox}}$. This process resembles the tyrosinase reactivity as shown in Scheme 2.

Each of the copper atoms in **5** is coordinated by two nitrogen and three oxygen atoms in a slightly distorted square pyramidal fashion. The basal planes of the two square pyramids formed by two nitrogen and two oxygen atoms are linked by an edge. The Cu_2O_2 core formed by the two copper centers and the two oxygen atoms of the bridging hydroxyl group (whose presence was also confirmed by IR spectroscopy, ν_{OH} 3606 cm^{-1}) as well as the phenolate function of $\mathbf{L}^{\mathbf{ox}}$ is butterfly shaped with a torsion angle of 17° between Cu−O−Cu−O. The two apical positions are occupied by two oxygen atoms of a triflate anion with binding parameters that are expected for such bonds. Also, the other Cu−N and Cu−O bond lengths are in the expected

Scheme 2. Simplified Illustration of the Mechanism of the Ortho-Hydroxylation Process Catalyzed by the Enzyme Tyrosinase



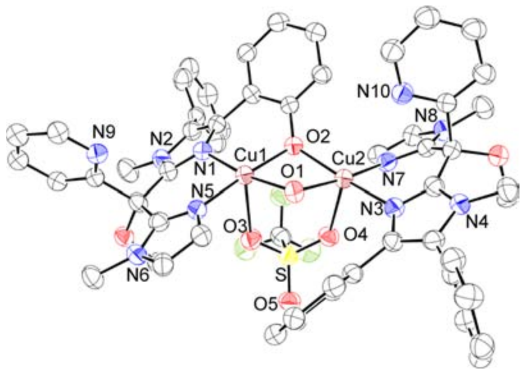


Figure 6. Molecular structure of the cation of $[\mathrm{L^{ox}Cu(OH)(OTf)CuL}](\mathrm{OTf})$, **5**. Hydrogen atoms are omitted for clarity. Selected bond lengths [Angstroms] and angles [degrees]: N1−Cu1 1.956(5), N5−Cu1 1.942(5), N3−Cu2 2.014(5), N7−Cu2 1.934(5), O1−Cu1 1.923(4), O2−Cu1 1.952(4), O1−Cu2 1.920(4), O2−Cu2 2.008(4), O3−Cu1 2.418(4), O4−Cu2 2.5031(44), S−O3 1.446(5), S−O4 1.453(4), S−O5 1.436(5); N1−Cu1−N5 91.3(2), N1−Cu1−O1 170.42(19), N1−Cu1−O2 92.70(18), N5−Cu1−O1 97.44(19), N5−Cu1−O2 175.75(18), Cu1−O1−Cu2 101.36(19), Cu1−O2−Cu2 97.31(17), N3−Cu2−N7 88.9(2), N3−Cu2−O1 97.11(18), N3−Cu2−O2 170.03(18), N7−Cu2−O1 173.65(19), N7−Cu2−O2 96.40(18), O1−Cu1−O2 78.66(17), O1−Cu2−O2 77.35(16).

ranges for N-chelating coordination complexes. The magnetic moment μ_{eff}/Cu of **5** was determined by the Evans method and found to be 1.38 μ_{B}/Cu. Compared to other complexes containing two copper centers bridged by phenoxido or hydroxido ligands this magnetic moment indicates a moderate antiferromagnetic coupling between the unpaired electrons.[17] This is consistent with other spectroscopic results obtained investigating **5**; the signals in its NMR spectrum appear paramagnetically shifted and broad, and the EPR spectrum shows a typical $\mathrm{Cu^{II}}$ signal (see Supporting Information).

In acetonitrile **5** undergoes further reactions to give **4** and a product that has been identified as $[\mathrm{L^{ox}{}_2Cu_2}](\mathrm{OTf})_2$ (**6**) spectroscopically and also by means of a single-crystal X-ray analysis (Figure 7). **6** is a dinuclear $\mathrm{Cu^{II}}$ complex containing the ligand $\mathbf{L^{ox}}$, in which the two copper atoms are bridged by two oxygen atoms belonging to the phenolate function of $\mathbf{L^{ox}}$.

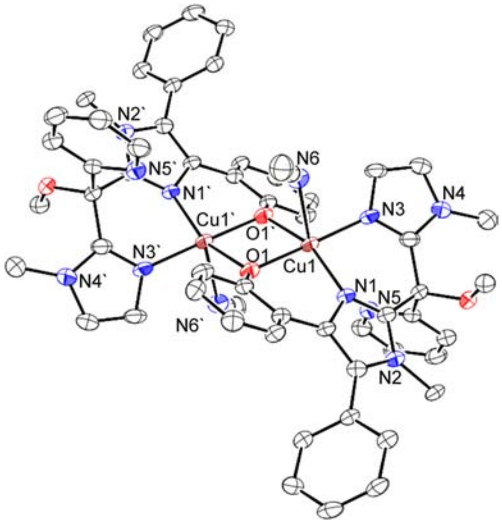
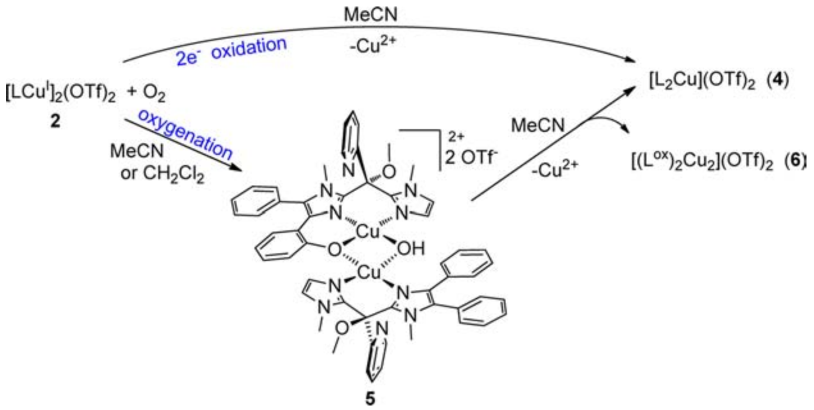


Figure 7. Molecular structure of the cation of $[\mathrm{L^{ox}{}_2Cu_2}](\mathrm{OTf})_2$, **6**. Hydrogen atoms are omitted for clarity. Selected bond lengths [Angstroms] and angles [degrees]: N1−Cu1 1.937(5), N3−Cu1 1.944(5), N6−Cu1 2.365(5), O1−Cu1 1.978(4), O1′−Cu1 1.954(4); N1−Cu1−N3 87.7(2), N1−Cu1−N6 106.26(19), N3−Cu1−O11 93.49(18), N1−Cu1−O1 90.42(19), N1−Cu1−O1′ 158.62(17), N3−Cu1−O1 178.08(19), N3−Cu1−O1′ 103.27(19), N6−Cu1−O1 87.35(16), N6−Cu1−O1′ 91.53(17), Cu1−O1−Cu1′ 101.58(18), O1−Cu1−O1′ 78.42(18).

Each copper center is coordinated in a slightly distorted square pyramidal fashion by these two oxygen atoms as well as by three nitrogen atoms of an acetonitrile molecule and two imidazolyl units of $\mathbf{L^{ox}}$. In contrast to **5**, the $\mathrm{Cu_2O_2}$ core in **6** is planar and the Cu−O−Cu angles are somewhat larger (both 101.58°) than those in **5** (97.31° and 101.36°). Both the Cu−O−Cu angle and the core structure have an influence on the coupling of the unpaired electrons in dinuclear copper cores.[18] Therefore, the magnetic moment μ_{eff}/Cu of **6** differs from that of **5** and was determined to be 0.94 μ_{B}, which is a typical value for complexes where two copper centers are strongly antiferromagnetically coupled through hydroxido and phenoxido ligands.[17b,18b] Consistent with this, **6** shows only a very

Scheme 3. Reactions within the $[LCu^I]_2(OTf)_2/O_2$ System



small signal in the EPR spectrum at 77 K (see Supporting Information). The signals in the NMR spectrum appear only slightly paramagnetically shifted.

Due to its tendency to undergo further reactions it is difficult to isolate **5** from reactions in acetonitrile in the pure form, although crystallization has only been achieved from acetonitrile solutions. However, performing the reaction of **2** with O_2 in CH_2Cl_2 leads to selective formation of **5** (Scheme 3). Remarkably, reaction of **1** and O_2 does not show any variations with the solvent; in acetonitrile as well as in dichloromethane it leads to **3** as the major reaction product, and ligand oxygenation occurs only to a small extent.

CONCLUSIONS

A novel, chiral ligand has been presented that was employed for synthesis of $[LCu]_2X_2$ and $[L_2Cu]X_2$ compounds ($X = PF_6$, OTf). Interestingly, the binding matrix, formed by two ligands with different configurations, is equally suited to coordinate either two Cu^I ions or one Cu^{II} ion, so that solid solutions can be generated. On the other hand, Cu^{II} ions can also coordinate two molecules of **L** with identical configurations, and corresponding complex cations are part of an equilibrium in solution. Which of the diastereomers crystallizes from a given solution is sensitively determined by the counteranions, the existence of other compounds in solution, and the presence of seeds. The reactivity of $[LCu]_2X_2$ compounds in contact with O_2 was found to depend on the X counterions, too. In the case of $X = PF_6$ almost exclusively the Cu^{II} oxidation product $[L_2Cu]X_2$ was formed, while for X = OTf an additional product could be isolated that in dichloromethane solution represents the main product: $[L^{ox}Cu(OH)(OTf)CuL](OTf)$, whose formation can be explained via an initial O_2 activation followed by C−H oxygenation. Hence, $[LCu]_2(OTf)_2$ shows tyrosine activity. Future research will build upon this and aim at the oxidation of exogenous substrates. Successful systems will then also be investigated with enantiomerically pure **L** to test its potential to induce stereoselective oxygenations.

ASSOCIATED CONTENT

Supporting Information

Molecular structure of 3^{rac}, of a solid solution of **2** and 4^{meso}, crystallographic details, X-ray crystallographic data in cif format, EPR spectra of **3**, **4**, **5**, and **6**, DOSY NMR spectra of **2**, and NMR spectrum of **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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