Supporting Information:

Cupric-Superoxo Mediated Inter-Molecular C-H Activation Chemistry

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Contents:

1. **Materials and Methods**

   All materials purchased were of highest purity available from Sigma-Aldrich Chemical, Wako Pure Chemical Industries, or Tokyo Chemical Indrusties (TCI) and used as received, unless specified otherwise. 2-Methyltetrahydrofuran (MeTHF) and tetrahydrofuran were distilled under an inert atmosphere from Na/benzophenone and degassed with argon prior to use. Pentane and acetonitrile were freshly distilled from calcium hydride under an inert atmosphere and degassed prior to use. BNAH was recrystallized from ethanol/water mixtures and vacuum dried prior to use. BNAD, BzIMH, and Cu(ACN)$_4$BArF were synthesized according to literature protocols, and their identity and purity were verified by elemental analysis and/or ^{1}H-NMR.[1,2] Synthesis and manipulations of copper salts were performed according to standard Schlenk techniques or in an MBraun glovebox (with O$_2$ and H$_2$O levels below 1 ppm). UV-Vis spectra were recorded with an HP Model 8453A diode array spectrophotometer equipped with a liquid nitrogen chilled Unisoku USP-203-A cryostat; kinetic measurements were maintained at -125°C ±1%. NMR spectroscopy was performed on Bruker 300 and 400 MHz instruments with spectra calibrated to either internal tetramethylsilane (TMS) standard or to residual protio solvent. EPR measurements were performed on an X-Band Bruker EMX-plus spectrophotometer equipped with a dual mode cavity (ER 4116DM) or Bruker EMX CW EPR controlled with a Bruker ER 041 XG microwave bridge operating at the X band (~9 GHz).

2. **Ligand Synthesis**
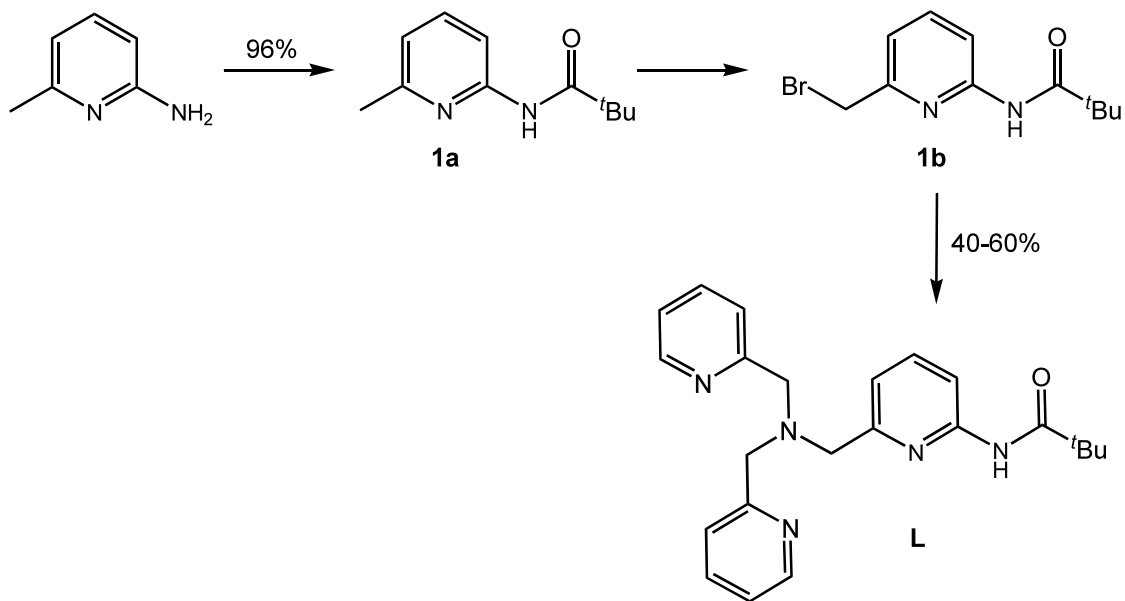
6-Pivaloylamino-2-picoline(1a): 6-Pivaloylamino-2-picoline was synthesized by a modified literature procedure.[3] 28.6 g (0.264 mol) of 6-Amino picoline was dissolved in a 500 ml flask containing 300 ml dichloromethane and 38.7 ml (0.278 mol)triethylamine. The flask was capped with a rubber septum and chilled in an ice bath and then was kept at 0°C for 30 min under argon with constant stirring. A mineral oil bubber was attached to the system as an outlet, then 34.2 ml (0.278 mol) of trimethyl acetyl chloride was added dropwise over 30 min. After complete addition of the acid chloride, the solution was allowed to react at 0°C for two hours, following which the flask was removed from the ice bath and the reaction stirred at room temperature for an additional 2 hours. The resulting mixture was filtered through a glass frit and the solid washed with hexane. The filtrates were pooled and solvent was removed under reduced pressure yielding a white solid, which was passed through an alumina plug washed with dichloromethane (DCM). Removal of DCM yielded 49.0g(96%) of 6-Pivaloylamino-2-picoline as a white solid. TLC: R_f=0.67 (silica, 50:50 Ethyl acetate:Hexanes). ^{1}H-NMR (CDCl$_3$): 8.06-8.03(d, 8Hz, 1H), 8.01(s, 1H), 7.60-7.55(t, 8Hz, 1H), 6.89-6.86(d, 8Hz, 1H), 2.45(s, 3H), 1.32(s, 9H).

Bis(pyrid-2-ylmethyl){[6-(pivalamido)pyrid-2-yl]methyl}amine(L): Bis(pyrid-2-ylmethyl){[6-(pivalamido)pyrid-2-yl]methyl}amine was synthesized by a modified literature method. [4] 6-Pivaloylamino-2-picoline(6.0g 31.2mmol)**1a**, and N-bromosuccinimide (NBS) (5.83g 32.08mmol), along with 100 mg Azobisisobutyronitrile(AIBN), were added to a two neck 250 ml round bottom flask connected to a reflux condenser and flushed with argon. 150 ml of degassed CCl$_4$ was added to the flask; the reaction mixture was refluxed for 8 hours under argon. The solution was then cooled to room temp and the solvent removed under reduced pressure, yielding a brown solid. The resulting solid was dissolved in 100 ml ethyl acetate (EtOAc) and passed through a short silica column; approximately 250-350 ml of additional EtOAC was passed though the column until all mono-brominated material was eluted [R_f = 0.78 (silica, 50:50 EtOAc:Hexanes)]. The EtOAc solution containing the mono-bromo product was used without purification in the next step. (Typical yields for mono-bromination were 40-60%) To the above EtOAC solution, 2,2'-Dipicolylamine (3.11g, 15.6mmol) and diisopropylethylamine (4.03g, 31.2 mmol) were added and the solution was stirred overnight at room temperature. Reaction progress was monitored via TLC and more 2,2'-Dipicolylamine was added to the solution if necessary. EtOAc was removed via reduced pressure after the reaction was complete, affording a brown oil. The residue was dissolved in an aqueous sodium carbonate solution and extracted into DCM. The organic layer was dried over sodium sulfate and the solvent removed by rotary evaporation. The resulting oil was chromatographed on a column of 1000 ml Si using first 1:2 EtOAc:Hexane to elute unreacted dibromo material and **1a**, followed by 2:1 EtOAc:Hex to elute **L,** which was isolated as a tan solid following removal of solvent. Overall yield from **1a** to **L** ranged from 40-60%. TLC: R_f= 0.25 (alumina, 50:50 EtOAc:hexane); R_f = 0.6 (alumina, 100% EtOAc). ^{1}H-NMR (CDCl$_3$): 8.56-8.54 (d, 4.8Hz, 2H), 8.12-8.10(d, 8Hz, 1H), 8.00(s, 1H), 7.70-7.65(m, 3H),

7.60-7.57(d, 8Hz, 1H), 7.32-7.30(d, 7.2Hz, 1 H), 7.19-7.152(t, 6.4Hz, 2H), 3.90(s, 4H), 3.79(s, 2H), 1.35(s, 9H).

3. **Synthesis of LCu(I) BArF (1)**

In a 100 ml schlenk flask located in the glove box, 174.6 mg of Cu(ACN)$_4$BArF was dissolved in 5 ml of 20% acetonitile in THF. 75 mg (0.192 mmol) of **L** dissolved in approximately 3 ml of THF was added to the copper solution, resulting in an immediate color change from colorless to red-orange. This solution was allowed to stir for 30 min at which time approximately 80 ml of degassed pentane was added to the solution, causing precipitation. After 45 min the supernatant was decanted and the solid removed from the glove box and dried under vacuum to afford 180 mg of a bright orange solid. (83% yield) Elemental analysis: (C$_{47}$H$_{27}$BCuF$_{20}$N$_5$O) Calculated: C(49.86) H(2.40) N(6.19); found: C(49.85) H(3.05) N(5.88).

4. **Crystal Structure of LCu(I) BArF**

Crystals suitable for X-ray analysis were grown from the mother liquor described in section 1-3, allowed to stand for 48 hrs.
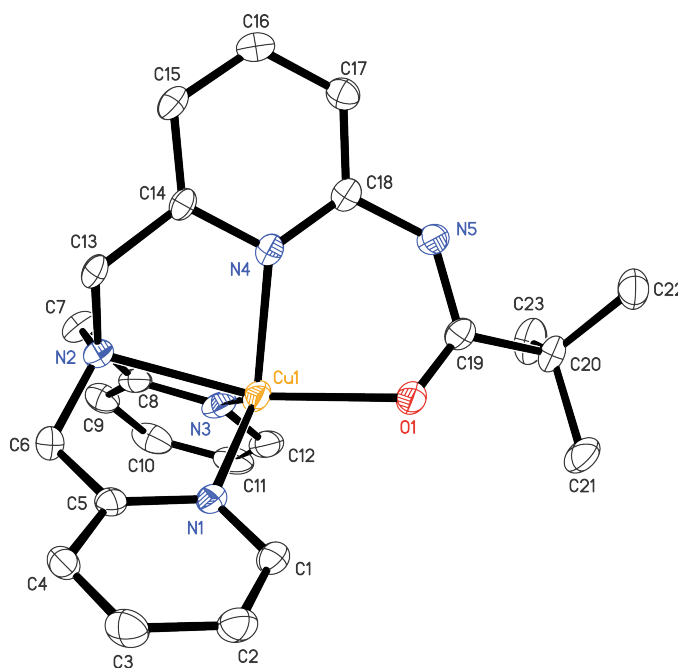
Cationic Portion of LCu(I) BArF; $\tau = 0.5958$ ($\tau = 1.00$ for a perfect trigonal-bipyramid and $\tau = 0.00$ for a perfect square-pyramid.[5] Selected bond lengths (Å) and angles (°) are given below:

Selected Bond Lengths and Angles	
Atoms	Bond Length(Å)
N1-Cu1	2.022
N2-Cu1	2.281
N3-Cu1	2.005
N4-Cu1	2.119
O1-Cu1	2.190
Bond Angle (^{0})	
N1-Cu1-O1	97.54
N1-Cu1-N2	80.24
N1-Cu1-N3	121.23
N1-Cu1-N4	117.73
N2-Cu1-O1	156.98
N2-Cu1-N3	90.51
N2-Cu1-N4	78.80
N3-Cu1-O1	119.94
N4-Cu1-O1	82.16

5. EPR Preparation and Procedure for 1

EPR experiments were done on 1 mM solutions of **L**Cu(I) BArF which were oxygenated at -130°C in a liquid nitrogen/pentane bath. EPR on this sample showed no signal in both // and ⊥ modes.

6. Methods for Kinetic Studies of Substrate Oxidation

2.5 ml of a 0.5 mM solution of [**L**Cu^{I}][BArF] was transferred to a modified schlenk cuvette, equipped with a glass sidearm and 14/20 glass joint, and was diluted with 600 ul of a 2-MeTHF solution containing varying amounts of substrate. The cuvette was sealed with a septum and secured with a plastic zip tie. This cell was transferred to the pre-cooled cryostat and allowed to chill at -125°C with a minimum of 20 minutes allowed for equilibration prior to oxygenation. Kinetic measurements were started followed by exposing the sample to a gentle stream of dioxygen, vented out through a needle, for 30-40 seconds.   Pseudo first-order fitting was performed on the decrease of the 741 nm absorbance(BNAH) or 410 (BzImH) band of **1**. Second order rate constants were obtained by plotting the pseudo first order rate constant k_{obs} vs substrate concentration.
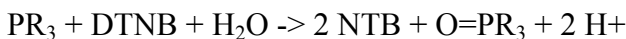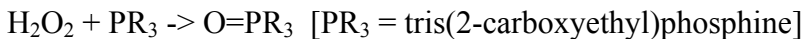
7. **BNAH Oxidation Quantification**

A typical experiment is described below: In a 50 ml schlenk flask 10.4 mg of PV-TMPA Cu(I) BArF and 26.2 mg BNAH(13.3eq) were dissolved in 20 ml MeTHF and capped with a septum secured with copper wire. The flask was placed in a Pentane/$N_2(l)$ bath for 25 minutes to allow for temperature equilibration. After 25 minutes dry dioxygen was gently bubbled through the solution for 45 seconds and the mixture was allowed to react for 2.5 hours at -130°C. After 2.5 hours, 100 uL of a 101 mM HCl solution(1.1eq) in diethylether was added to quench the reaction at-130°C. The solution was then allowed to warm up to room temp under vacuum and all solvent was removed, yielding a green solid. The ^{1}H-NMR of the resulting green residue was taken in DMSO-D_6 and BNA$^+$ integration was compared to 1,2-dichloroethane as an internal standard.

8. **Hydrogen Peroxide Quantification**

In a typical experiment, a Schlenk cuvette was charged with 2.5 ml of a 0.5 mM solution of [LCu^I][BArF] in MeTHF which was then diluted with 600 ul of a MeTHF solution of BNAH, to give a final concentration of Cu(I) ~ 400 uM and substrate in approximately 10-25 fold excess. This cell was transferred to the cryostat and cooled to -125°C. The solution was then oxygenated with pure, dry O_2 and the reaction of Cu^{II}-superoxo with BNAH allowed to proceed to completion (at least six half-lives), as followed by UV-Vis spectroscopy. The reaction was then quenched (at low temperature) with excess ethereal HCl (~ 50 eq, per Cu). The cuvette was removed from the cryostat and diluted with THF to a volume < 5 mL (r.t.) to complete precipitation of all Cu, ligand, and substrate salts. The suspension was filtered through a fine frit and the filtrate diluted to a final volume of 5 mL with THF, used to wash the filtrand. To 1 mL liter of this solution was added 3 mL of MeOH, 1 mL of 500 mM phosphate buffer (pH = 7.4), 2 mL DI H2O, and 10 uL of a 25 mM stock solution of TCEP [tris(2-carboxylethyl)phosphine)] in 500 mM phosphate buffer. This mixture was allowed to incubate for at least 15 min. , after which time, 10 uL of a 50 mM stock solution of DTNB [5,5'-dithio-bis(2-nitrobenzoic acid)] was added, and the now yellow solution then diluted to a final volume of 10 mL with DI H_2O. The UV-Vis spectrum of this solution was then taken and the absorbance at 412 nm compared to that of a standard prepared as follows: 1 mL from a 3 mL MeTHF solution of ethereal HCl diluted to 5 mL with THF; 1 mL 500 mM phosphate buffer; 3 mL MeOH; 10 uL each of TCEP and DTNB stock solutions; and, finally, dilution to a final volume of 10 mL with DI H_2O.

The concentration of H_2O_2 in solution was determined by taking the difference in absorbance at 412 nm between the reaction sample spectrum and the standard (with only TCEP and DTNB, but no H_2O_2) spectrum and using the extinction coefficient (~ 14,000 M^{-1} cm^{-1}) of NTB (2-nitro-5-thiobenzoate) to back-calculate the amount of H_2O_2, according to the following scheme:[6]

$H_2O_2 + PR_3 \rightarrow O{=}PR_3$ [PR_3 = tris(2-carboxyethyl)phosphine]

$PR_3 + DTNB + H_2O \rightarrow 2\ NTB + O{=}PR_3 + 2\ H+$

The validity of this procedure was tested with H_2O_2 solutions of known concentrations.

9. rRaman Experimental Details

A 0.7mM copper solution was made by dissolving 3.9 mg of PV-TMPACu(I) BArF in 2-MeTHF to make a total 5 ml solution. 400 ul of the 0.7mM PV-TMPA solution was added to a 5mm NMR tube capped with an NMR septum. The NMR tubes were chilled in a Pentane/N_2(l) bath for at least 20 min prior to oxygenation. Oxygenation of the copper samples was achieved by slowly bubbling approximately 1.5 ml of dioxygen through the solution with a Hamilton gas-tight syringe equipped with a 3-way valve and needle outlet. After addition of dioxygen, the sample tubes were frozen in N_2(l), flame sealed and shipped in a dry shipper to Stanford University. Dioxygen, $^{16}O_2$ (OX UHP-300 Airgas) and $^{18}O_2$ (Icon 6393), were added to an evacuated Schlenk flask fitted with a septum for the oxygenation reactions described above. Resonance Raman spectra were obtained using a Princeton Instruments ST-135 back-illuminated CCD detector on a Spex 1877 CP triple monochromator with 1800 grooves/mm holographic spectrograph gratings. The excitation was at 413 nm and provided by Coherent I90C-K Kr$^+$ ion laser with incident power 5mW on the sample in a ~135° backscattering configuration. Sample concentration was 0.7mM in Cu and spectra were collected on the frozen MeTHF solutions in NMR tubes cooled to 77K in a liquid nitrogen finger Dewar (Wilmad). Background spectra of charcoal in NMR tubes were used for baseline subtraction. Peak intensities were determined relative to solvent bands.

10. Figure S(1): UV-Visible Spectrum of 1
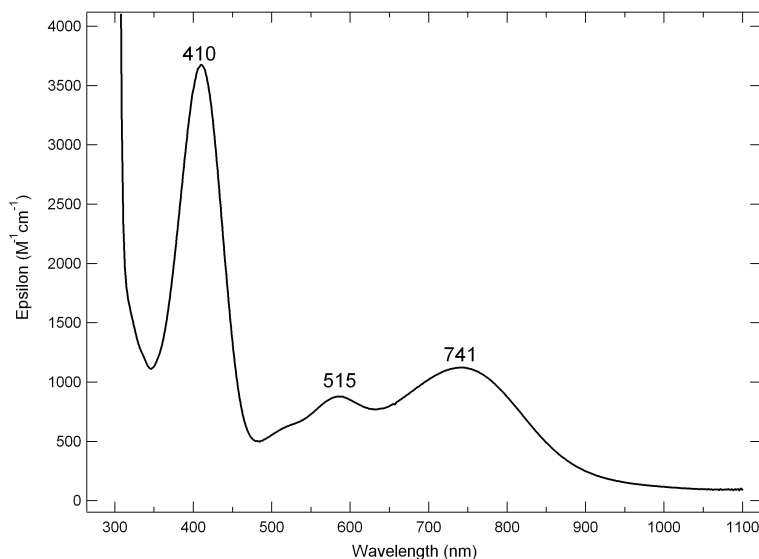
UV-Visible spectrum of **1** in MeTHF at -125°C

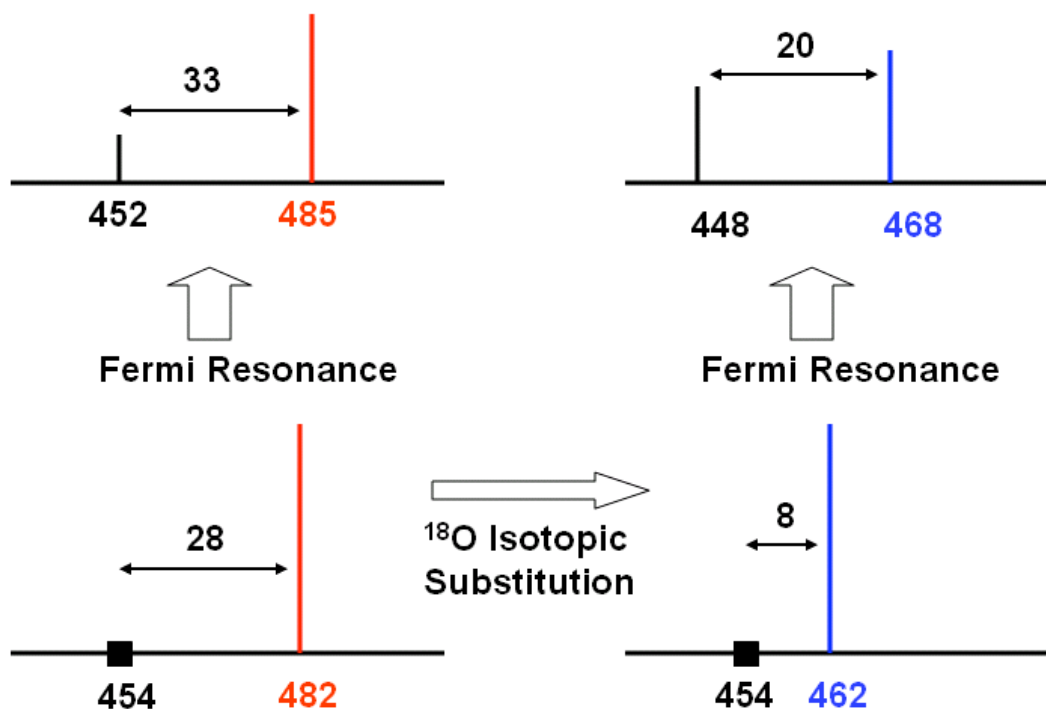## 11. Figure S(2): Fermi Resonance Analysis of the rR Data in CuO Region

Figure S(2) Bottom: Schematic illustration of the pre-interaction Raman peaks for the [16]O complex (red) and the [18]O complex (blue). Top: The observed result of Fermi interaction of a resonance enhanced ν(Cu-O) mode with a non-enhanced mode of the same symmetry and similar energy (black). All the frequencies are in the unit of cm^{-1}. See Refs 7-8 for more details.

12. Table S(3) and Figure S(4): DFT Calculations with Selected Bond Lengths with Optimized Geometries of 1 and TMPA Analouge

Spin-unrestricted DFT calculations were performed using Gaussian 03 program. The unrestricted B3LYP functional was used with 6-311G* basis set on critical atoms including Cu, superoxo, and N atoms coordinating to Cu; while 6-31G* basis set was used on all other atoms. The PCM method with a dielectric constant = 7.0, the value for MeTHF, was used to simulate the solvent effect. The largest Cu-N$_{equatorial}$ distance in the optimized geometries of **1** is 2.380 Å, which is for the bond between Cu and the coordinating N in the pyridine ring with the pivalamido group. This bond length is 0.27 Å longer than in $[Cu^{II}TMPA(O_2^-)]^+$. In order to test whether this distortion due to the steric effect of the pivalamido group has an effect on the frequencies, the $[Cu^{II}TMPA(O_2^-)]^+$ structure with four Cu-N fixed at the bond lengths of the values in the optimized structure of **1** was optimized and the frequencies were calculated. Structures of **1** with H-bonding to the alpha and beta oxygen of the superoxo moiety have been

modeled. The ground state is calculated to be a triplet in both cases; the S = 0 singlet state has almost the same optimized geometry as the S = 1 triplet ground state. After corrected to eliminate triplet-state spin contamination from the broken symmetry singlet excited state using the Yamaguchi formula $^1E = \dfrac{2\,^{BS}E - <S^2>_{BS}\,^3E}{2 - <S^2>_{BS}}$ (note*), the singlet-triplet energy splitting is calculated to be 1581.4 cm^{-1} (4.52 kcal/mol) for H-bonding with beta O structure and 1664.8 cm^{-1} (4.76 kcal/mol) for H-bonding with alpha O structure. In order to test the inductive effect of the pivalamido group, a modified structure of **1** with the pivalamido group on the para position has also been modeled. DFT-calculated bond lengths and frequencies are listed in Table S3.
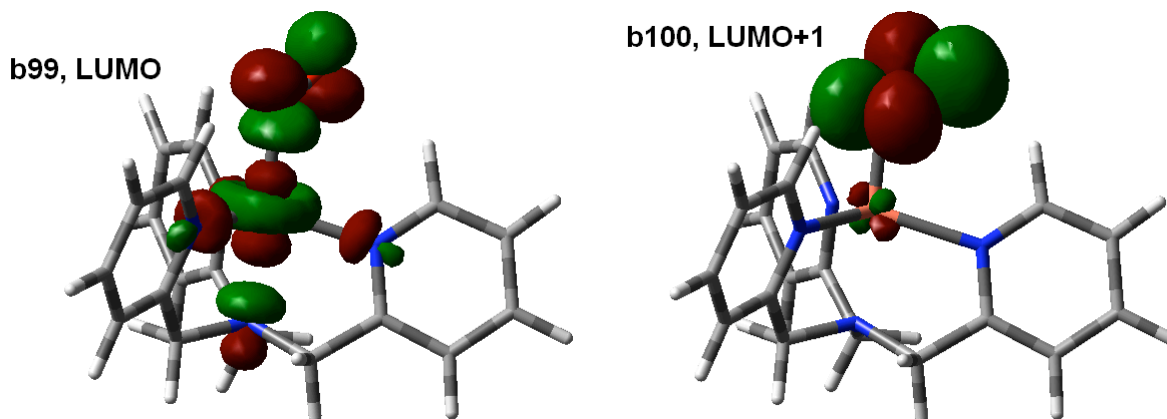
Note*: Yamaguchi, K.; Jensen, F.; Dorigo, A.; Houk, K. N. *Chem. Phys. Lett.* **1988**, *149*, 537–542.

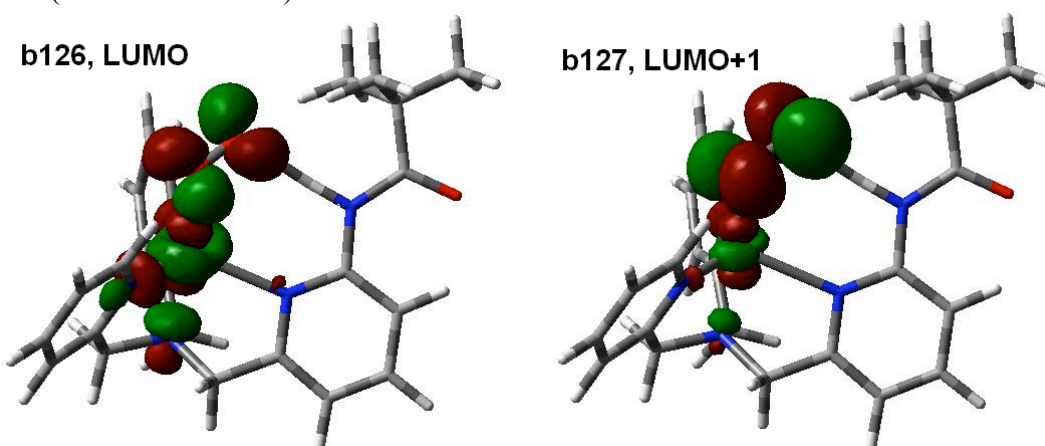**Table S(3)** Important Bond Lengths in DFT Optimized Geometries and DFT Calculated Frequencies

	Bond Length (Å)		Frequency (cm^{-1})	
	Cu-O	O-O	Cu-O	O-O
[Cu^{II}TMPA(O$_2^-$)]$^+$	1.925	1.294	456.9	1211.4
[Cu^{II}TMPA(O$_2^-$)]$^+$ (Cu-N bonds fixed at the bond lengths in the optimized structure of **1**)	1.924	1.296	467.1	1206.3
1 (H-bond to beta O)	1.920	1.299	467.4	1220.2
1, the pivalamido group at the para position	1.927	1.295	455.9	1214.8
1 (H-bond to alpha O)	1.929	1.297	457.7	1216.2

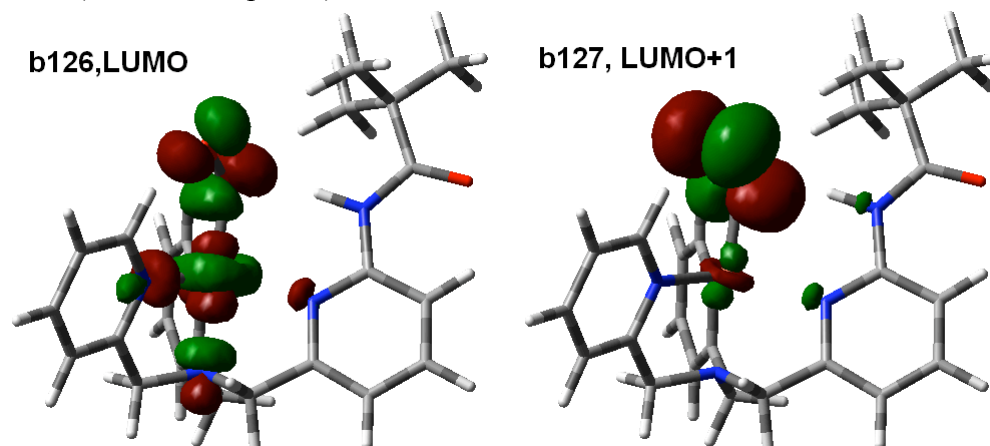**Figure S(4)** Optimized geometries with the two half-occupied molecular orbitals: beta LUMO and beta LUMO+1.

A. $[Cu^{II}TMPA(O_2^-)]^+$

b99, LUMO

b100, LUMO+1

B. 1 (H-bond to beta O)

b126, LUMO

b127, LUMO+1

C. 1 (H-bond to alpha O)

b126,LUMO

b127, LUMO+1

S11

# 13. Table S(5) Resonance Raman Table of Reported Cupric Superoxo Species

Table S5

Resonance Raman Table of Reported Cupric Superoxo Species

| Supporting Ligand	Superoxide Binding Mode	$\nu(^{16}O\text{-}^{16}O)/cm^{-1}$ $(\Delta(^{18}O)/cm^{-1})$	$\nu(Cu\text{-}^{16}O)/cm^{-1}$ $(\Delta(^{18}O)/cm^{-1})$	Refs.
L (TPA$^{6'\text{-NHPv}}$)	η^1	1130 (63)	482 (20)	This Work
TPA^{NMe2}	η^1	1121 (63)	472 (20)	1
Tren^{Me,Bn}	η^1	1120 (61)	474 (20)	2
Tren^{Me,Me}	η^1	1122		2
Tren^{TMG}	η^1	1117 (58), 1122[a]		3-4
Tren^{TMG}	η^1	1120 (63)	435 (20)	5
Pyridyl-diaza-cyclooctane tridentate	η^1	1033 (65)	457 (15)	6
DPH$_3$	η^1	964 (55)[a]		7
Pyridyl diamido dianionic tridentate	η^1	1104(60)		8
HB(3-^{t}Bu-5-^{i}Prpz)$_3$	η^2	1112 (52)[a]		9
HB(3-Ad-5-^{i}Prpz)$_3$	η^2	1043 (59)	554 (20)	10
TACN^{PhOH}	η^2	1120 (62)	450 (8), 422 (5)	11

[a]IR Data

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14. Figure S(6): Kinetic Trace of 1 with BzIM
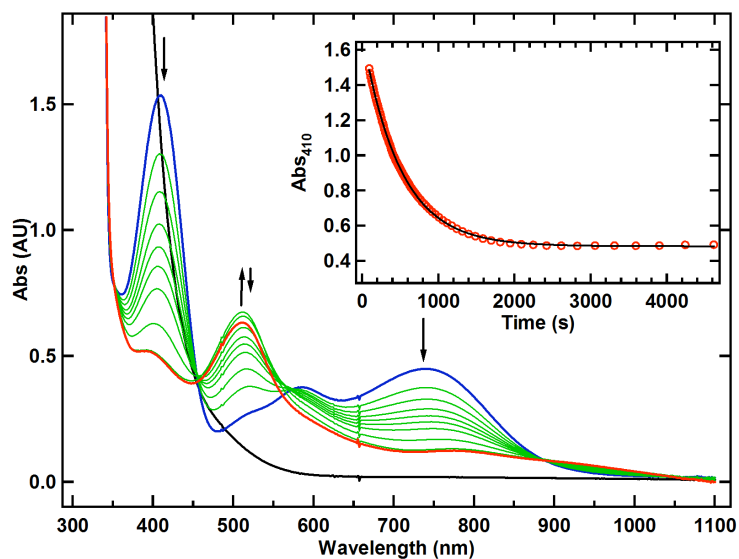
S(6). Kinetic measurement of the oxidation of 26.3 mM BzIMH by **1**. Black-LCu(I), Blue-**1**, Red- Final spectra at -125 °C exposure Insert exponential fit to decay of 410 nm.

15. Overview of Proposed DβM/PHM Mechanisms
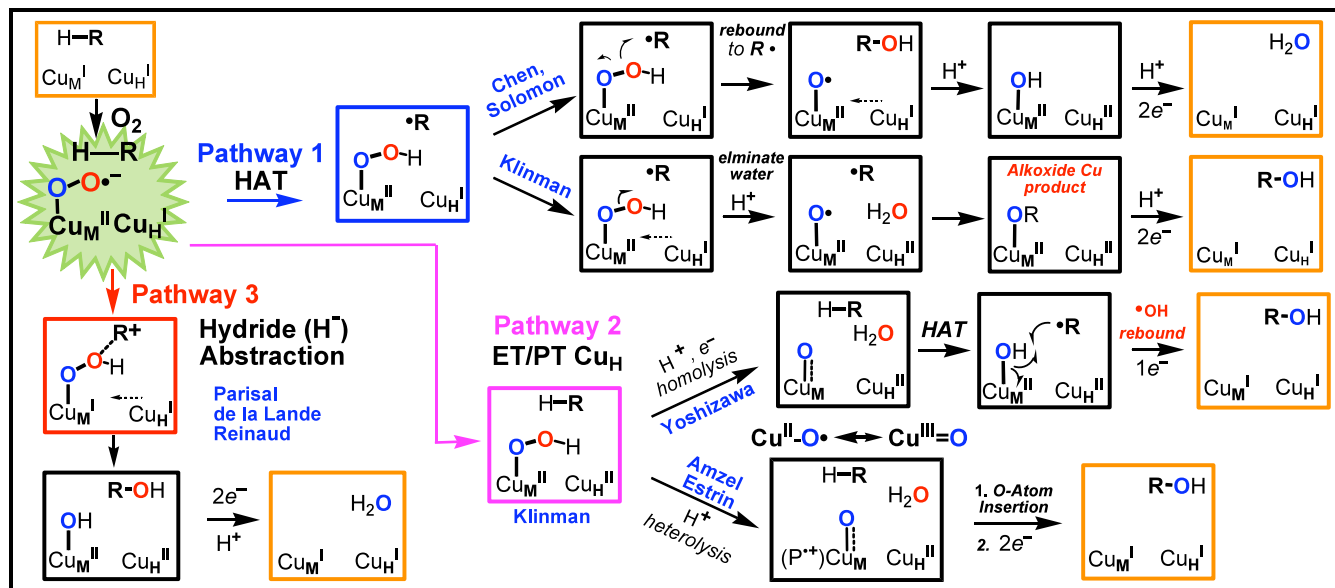
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