Supporting Information for

Mechanism of Alcohol Oxidation Mediated by Copper(II) and Nitroxyl Radicals

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I. General Considerations

All commercially available compounds were purchased and used as received. ^{1}H and ^{13}C NMR spectra were recorded on Bruker or Varian 300 or 400 MHz spectrometers. Chemical shift values are given in parts per million relative to internal TMS or residual peaks in deuterated solvents. NMR spectra were plotted with wxMacNUTS v1.0.2 (Acorn NMR, Inc. 2007) and MestReNova v7.1.2 (MestreLab Research S. L. 2012). Flash chromatography was performed using SiliaFlash® P60 (Silicycle, particle size 40-63 μm, 230-400 mesh). Gas chromatographic analyses of the reactions were conducted with a Shimadzu GC-17A gas chromatograph with Stabiliwax-DB column, using trimethyl-(phenyl)silane as an internal standard.

II. Synthesis/Characterization of Radical Probe Substrates

Cyclopropyl carbinol and cyclobutanol were purchased from Sigma-Aldrich and used as received. All other chemicals were used as received or purified using standard techniques.

1-Phenylcyclopropylmethanol. A modified literature procedure was used.[1] Under an atmosphere of N_2, diiodomethane (6.5 g, 24.5 mmol) was added dropwise to a 50 mL solution of diethylzinc in methylene chloride (13 mmol) at -10 °C and gradually warmed to room temperature. Cinnamyl alcohol (1.19 g, 10.35 mmol) and catalytic $Ti(O^{i}Pr)_4$ (0.17 g, 0.6 mmol) were added sequentially, and the reaction mixture was stirred overnight. The reaction was quenched with NH_4Cl, and extracted with Et_2O, washed with brine, filtered through a celite pad, and then purified by silica column chromatography (4:1 hexanes:ethyl acetate).[1]H NMR spectrum matched literature: (400 MHz) ^{1}H NMR (400 MHz, chloroform-*d*) δ δ 0.91-1.00 (m, 2H), 1.42-1.50 (m, 1H), 1.62 (s, 1H, -OH), 1.81-1.86 (m,1H), 3.58-3.67 (m, 2H), 7.07-7.29 (m, 5H, Ar-H).

2,3-*cis*-Diphenylcyclopropylmethylcarbinol was synthesized according to literature procedure.[2] ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.15 - 6.97 (m, 6H), 7.00 - 6.86 (m, 4H), 3.85 (d, *J* = 6.6 Hz, 2H), 2.42 (d, *J* = 5.6 Hz, 2H), 2.10 (tt, *J* = 5.6, 6.6 Hz, 1H), 1.66 -1.53 (br, 1H).

2-Allyloxybenzyl alcohol. 2-Hydroxybenzaldehyde (1.8 mL, 16.9 mmol) was combined with allylbromide (1.8 mL, 20.8 mmol) in acetone with potassium carbonate (1.5 g) and stirred at room temperature to afford the 2-allyloxybenzaldehyde (2.35 g, 85% yield; 45% yield after column chromatography). The aldehyde (100 mg, 0.61 mmol) was reduced with sodium borohydride (34.1 mg, 0.9 mmol) to afford the alcohol product in 95% yield. The reaction was quenched with 6 M HCl, extracted with ether and dried over $MgSO_4$. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.48 - 7.33 (m, 1H), 7.32 - 7.14 (m, 4H), 6.92 (q, *J* = 7.1 Hz, 2H), 6.83 (dd, *J* = 14.1, 8.2 Hz, 2H), 6.14 - 5.86 (m, 2H), 5.49 - 5.33 (m, 2H), 5.32 - 5.17 (m, 2H), 5.11 (s, 1H), 4.70 (s, 2H), 4.62 - 4.47 (m, 5H).

III. Experimental Procedure for Alcohol Oxidations

General procedure for aerobic alcohol oxidation. The oxidation of the alcohols in Table 1 was conducted as follows. In a 20 mm culture tube, 0.2 mmol of the alcohol was combined with 0.01 mmol $[Cu(MeCN)_4]OTf$, 0.01 mmol 2,2'-bipyridyl, 0.01 mmol TEMPO, and 0.02 mmol NMI in 2 mL of anhydrous MeCN. The culture tube was fitted with a septum and an O_2 balloon and magnetically stirred. The reactions were monitored by TLC and color change. Upon completion of the reactions, the solutions were diluted with ethyl acetate and filtered through a silica plug. Solvent was removed by rotary evaporation and solids were dissolved in $CDCl_3$ for ^{1}H NMR analysis with trimethoxybenzene as an internal standard.

Procedure for aerobic alcohol oxidation of cyclopropylmethanol and cyclobutanol. The reactions of these alcohols were carried out in an identical fashion to the general method above,

with the following modifications. MeCN-d_3 was used as the reaction solvent and acetone-d_6 was used instead of EtOAc for the workup with the silica plug. The reaction mixtures were submitted to ^{1}H and ^{13}C NMR analysis following the silica plug without evaporation to mitigate loss of volatile products and starting materials.

Aldehyde product characterization. All aldehydes are known compounds and have been previously characterized. ^{13}C NMR spectra were obtained for compounds that required confirmation of identity for compounds with few ^{1}H resonances or resonances that overlapped with solvent peaks.

1-Phenylcycloproprylcarboxaldehyde.[3] ^{1}H NMR (400 MHz, chloroform-*d*) δ 9.25 (d, *J* = 4.6 Hz, 1H), 7.22 (dd, *J* = 8.1, 6.7 Hz, 2H), 7.19 - 7.10 (m, 1H), 7.07 - 7.01 (m, 2H), 2.55 (ddd, *J* = 8.5, 6.6, 3.9 Hz, 1H), 2.10 (dd, *J* = 8.5, 4.3 Hz, 1H), 1.65 (dt, *J* = 9.6, 5.0 Hz, 1H), 1.45 (ddd, *J* = 8.1, 6.6, 4.9 Hz, 1H).

2,3-*cis*-Diphenylcyclopropylmethylcarboxaldehyde.[4] ^{1}H NMR (400 MHz, chloroform-*d*) δ 9.64 (d, *J* = 4.1 Hz, 1H), 7.14 (m, 6H), 6.99 - 6.89 (m, 4H), 3.18 (d, *J* = 5.1 Hz, 2H), 2.83 (q, *J* = 4.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.67, 134.86, 128.95, 128.13, 126.81, 77.60, 77.28, 76.96, 36.86, 33.50.

2-Allyloxybenzylaldehyde.[5] ^{1}H NMR (400 MHz) ^{1}H NMR (400 MHz, chloroform-*d*) δ 10.54 (s, 1H), 7.84 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.53 (ddd, *J* = 8.8, 7.4, 1.8 Hz, 1H), 7.19 - 6.77 (m, 2H), 6.08 (ddt, *J* = 17.3, 10.4, 5.1 Hz, 1H), 5.46 (dd, *J* = 17.2, 1.7 Hz, 1H), 5.39 - 5.29 (m, 1H), 4.66 (dt, *J* = 4.9, 1.5 Hz, 3H).

Cyclopropylcarboxaldehyde[6] ^{1}H NMR (400 MHz, acetone-d_6) δ 8.83 (d, *J* = 6.0 Hz, 1H), 1.77 (sext, *J* = 6.1 Hz, 1H), 1.05 (d, *J* = 6.2 Hz, 4H). ^{13}C NMR (101 MHz, Acetone-d_6) δ 201.99, 23.20, 6.93, 1.52.

Cyclobutanone[7] Yield: 90.1 % ^{1}H NMR (500 MHz, Chloroform-d) δ 3.09 (t, J = 8.2 Hz, 4H), 2.01 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.65, 47.97, 21.30, 9.95.

IV. Computational Details

All geometries were fully optimized via density functional theory[8] using the OPBE functional, MDF10 basis set (plus three additional uncontracted f orbitals having exponents 5.100, 1.275, and 0.320) and effective core potential[9] for copper and 6-31g(d) basis set for all other atoms using Gaussian09.[10] The natures of stationary points were verified by computing analytical frequencies of all structures. Transition state vibrations were verified as connecting reactants and products by viewing normal mode vibrations with imaginary frequencies and also by performing intrinsic reaction coordinate (IRC) analyses, where necessary. Partition functions were used in the computation of 298 K thermal contributions to free energy using the ideal gas, rigid-rotor and harmonic oscillator approximation.[11] Single point energies were calculated at the optimized geometries, employing the same basis set for copper and the 6-311+g(d) basis set for other atoms. The SMD continuum solvation model was used to account for the effects of acetonitrile.[12] Free energies were computed assuming a 1 M concentration for all species, except for acetonitrile (solvent), for which a concentration of 19.15 M was used. The non-standard state solvent concentration contribution to the free energy at 298 K was computed according to $\Delta G = \Delta G^0 + RT \cdot \ln(K)$ and had magnitude 2.95 kcal/mol. Temperature effects were accounted for by computing standard-state free energies and using these data in the equation $\Delta G = \Delta H - T\Delta S$, using 298 K as the temperature. All free energies quoted are at 25 °C (298 K), unless otherwise specified.

V. Derivation of Rate Law (Equation 1)

$$Cu^{II}(OH) + RCH_2OH \underset{}{\overset{K_1}{\rightleftharpoons}} Cu^{II}(OCH_2R) \quad \text{(S1)}$$

$$Cu^{II}(OCH_2R) + TEMPO \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} Cu^{II}(TEMPO)(OCH_2R) \quad \text{(S2)}$$

$$Cu^{II}(TEMPO)(OCH_2R) \xrightarrow{k_3} Product \quad \text{(S3)}$$

$$d[product]/dt = k_3[Cu^{II}(TEMPO)(OCH_2R)] \quad \text{(S4)}$$

Apply the steady-state approximation for $[Cu^{II}(TEMPO)(OCH_2R)]$:

$$d[Cu^{II}(TEMPO)(OCH_2R)]/dt = 0 = -k_3[Cu^{II}(TEMPO)(OCH_2R)] - k_{-2}[Cu^{II}(TEMPO)(OCH_2R)] + k_2[Cu^{II}(OCH_2R)][TEMPO]$$

which may be rearranged as follows:

$$[Cu^{II}(TEMPO)(OCH_2R)] = \frac{k_2[Cu^{II}(OCH_2R)][TEMPO]}{k_3 + k_{-2}} \quad \text{(S5)}$$

Expressions for $[Cu]_{tot}$ and $[Cu^{II}(OCH_2R)]$:

$$[Cu]_{tot} = [Cu^{II}(OH)] + [Cu^{II}(OCH_2R)] \quad \text{(S6)}$$

$$K_1 = \frac{[Cu^{II}(OCH_2R)]}{[Cu^{II}(OH)][RCH_2OH]} \quad \text{(S7)}$$

Insert expression for $[Cu^{II}(OH)]$ from eq S6 into eq S7:

$$K_1 = \frac{[Cu^{II}(OCH_2R)]}{([Cu]_{tot} - [Cu^{II}(OCH_2R)])[RCH_2OH]}$$

Rearrange and solve for $[Cu^{II}(OCH_2R)]$:

$$K_1[Cu]_{tot}[RCH_2OH] - K_1[Cu^{II}(OCH_2R)][RCH_2OH] = [Cu^{II}(OCH_2R)]$$

$$K_1[Cu]_{tot}[RCH_2OH] = [Cu^{II}(OCH_2R)](1 + K_1[RCH_2OH])$$

$$[Cu^{II}(OCH_2R)] = \frac{K_1[Cu]_{tot}[RCH_2OH]}{1 + K_1[RCH_2OH]} \quad \text{(S8)}$$

Insert expression for $[Cu^{II}(OCH_2R)]$ from eq S8 into eq S5:

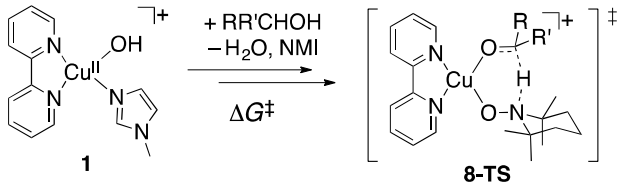
$$[Cu^{II}(TEMPO)(OCH_2R)] = \frac{K_1 k_2 [Cu]_{tot}[TEMPO][RCH_2OH]}{(k_3 + k_{-2})(1 + K_1[RCH_2OH])} \quad \text{(S9)}$$

Eq S9 can be inserted directly into eq S4:

$$\frac{d[product]}{dt} = \frac{K_1 k_2 k_3 [Cu]_{tot}[TEMPO][RCH_2OH]}{(k_3 + k_{-2})(1 + K_1[RCH_2OH])} \quad (1)$$

VI. Representative Comparison of Different Functionals: OPBE, M06-L and B3LYP.

Table S1. Functional Dependence of the Free Energies of the Hydrogen-Transfer Transition State **8-TS** with Various Alcohols, Relative to $[(bpy)Cu(OH)(NMI)]^+$ **1.**



	$\Delta G^{\ddagger}$ (kcal/mol)[a]		
Functional	**^{n}PrOH**	**BnOH**	**^{i}PrOH**
OPBE	16.9	15.8	23.2
M06-L	7.8	4.0	10.6
B3LYP	28.4	27.2	33.8

The values in Table S1 show that the M06-L functional leads to energies much lower than those observed experimentally, while B3LYP leads to energies much higher than those observed experimentally.

VI. Cu^{II}/AZADO-Mediated Alcohol Oxidation.

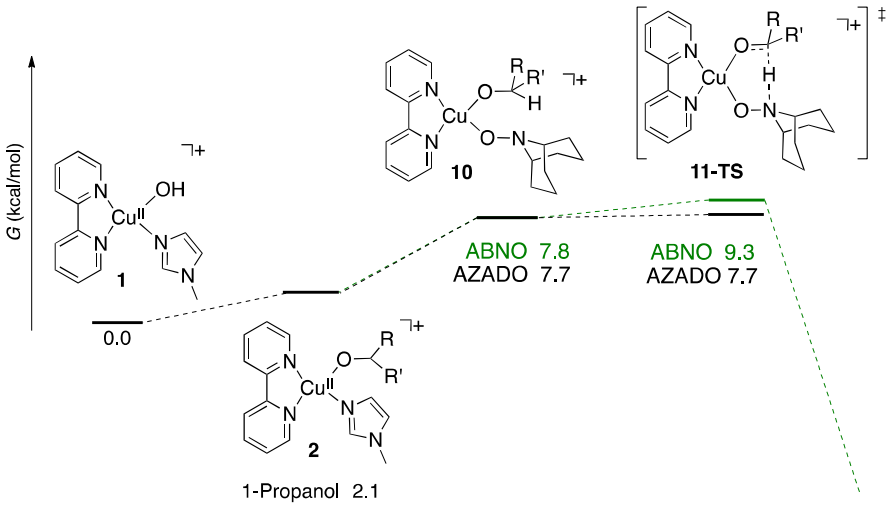


Figure S1. Comparison of Cu^{II}/ABNO- and Cu^{II}/AZADO-mediated oxidation of 1-propanol.

VII. Tabulated Computed Energies

Structure	E	H	G	Thermal Correction	G(solv)	G (corr)
TEMPO	-483.5029889	-483.229508	-483.279567	0.223422	-483.615294	-483.391872
TEMPOH_OH	-484.1034522	-483.818019	-483.867045	0.236407	-484.214680	-483.978273
TEMPOH_NH	-484.088402	-483.802616	-483.851581	0.236821	-484.210056	-483.973235
ABNO	-443.0027932	-442.778494	-442.821317	0.181476	-443.116434	-442.934958
ABNOH_OH	-443.6090618	-443.373107	-443.415663	0.193399	-443.71986463	-443.5264656
ABNOH_NH	-443.6090618	-443.373107	-443.415663	0.193399	-443.714988	-443.521589
AZADO	-481.1120882	-480.881059	-480.922779	0.189309	-481.2320308	-481.0427218
H_2O	-76.37273419	-76.347753	-76.369201	0.003534	-76.413015	-76.409481
nPrOH	-194.2569335	-194.142506	-194.176707	0.080226	-194.314018	-194.233792
iPrOH	-194.2620767	-194.148238	-194.181997	0.080079	-194.319199	-194.239120
BnOH	-346.6137854	-346.47401	-346.514461	0.099324	-346.706133	-346.606809
NMI	-265.4216195	-265.317044	-265.352366	0.069254	-265.498291	-265.429037
MeCN	-132.6947901	-132.645288	-132.6739	0.02089	-132.736625	-132.715735
Propanal	-193.0551716	-192.96654	-192.998509	0.056663	-193.112210	-193.055547
Acetone	-193.0680722	-192.97863	-193.013333	0.054739	-193.125753	-193.071014
Benzaldehyde	-345.4220618	-345.30622	-345.344323	0.077739	-345.510197	-345.432458
1	-1033.97531560	-1033.682788	-1033.755034	0.220282	-1034.248079	-1034.027797
2-OnPr	-1151.856328	-1151.475034	-1151.558562	0.297766	-1152.146571	-1151.848805
2-OiPr	-1151.859532	-1151.478775	-1151.560971	0.298561	-1152.149280	-1151.850719
2-OBn	-1304.213693	-1303.806785	-1303.89684	0.316853	-1304.540964	-1304.224111
3-OnPr	-1019.11719	-1018.791925	-1018.872034	0.245156	-1019.375457	-1019.130301
3-OiPr	-1019.11719	-1018.791926	-1018.872034	0.245156	-1019.375457	-1019.130301
3-OBn	-1171.473487	-1171.122578	-1171.208046	0.26544	-1171.768732	-1171.503292
4^{NMI}-OnPr	-1635.350123	-1634.7009	-1634.809793	0.54033	-1635.736764	-1635.196434
4^{NMI} -OiPr	-1635.364088	-1634.7133	-1634.827313	0.536774	-1635.748247	-1635.211473
4^{NMI} -OBn	-1787.714348	-1787.037995	-1787.15902	0.555328	-1788.133268	-1787.577940
4^{MeCN} -OnPr	-1502.62514	-1502.03044	-1502.137883	0.487256	-1502.979808	-1502.492552
4^{MeCN} -OiPr	-1502.629759	-1502.033856	-1502.143624	0.486135	-1502.982743	-1502.496608

4^{MeCN}-OBn	-1654.988359	-1654.366031	-1654.482029	0.50633	-1655.377197	-1654.870867
5	-1090.937591	-1090.610469	-1090.692624	0.244967	-1091.202861	-1090.957894
6^{nPr}	-1369.906513	-1369.356846	-1369.450120	0.456393	-1370.231454	-1369.775061
7-OnPr	-1369.924065	-1369.374621	-1369.466771	0.457294	-1370.247255	-1369.789961
7-OiPr	-1369.925073	-1369.37599	-1369.468194	0.456879	-1370.248136	-1369.791257
7-Obn	-1522.283677	-1521.709374	-1521.8061	0.477577	-1522.641223	-1522.163646
8-TS-OnPr	-1369.920672	-1369.375005	-1369.465881	0.454792	-1370.242726	-1369.787934
8-TS -OiPr	-1369.917472	-1369.372561	-1369.462517	0.454954	-1370.238246	-1369.783292
8-TS -OBn	-1522.283302	-1521.711651	-1521.807	0.476758	-1522.639609	-1522.162851
9	-1176.89102	-1176.432955	-1176.51164	0.379379	-1177.172227	-1176.792848
10-OnPr	-1329.444027	-1328.944267	-1329.029145	0.414882	-1329.76025	-1329.345368
10-OiPr	-1329.448041	-1328.948749	-1329.033322	0.414719	-1329.763841	-1329.349122
11-TS-OnPr	-1329.442411	-1328.946328	-1329.031109	0.411302	-1329.757468	-1329.346166
11-TS-OiPr	-1329.44652	-1328.950884	-1329.034466	0.412054	-1329.760854	-1329.3488
12	-1136.410394	-1136.000129	-1136.073307	0.337087	-1136.686171	-1136.349084
bpyCu_NMI_2	-1223.670397	-1223.286717	-1223.374374	0.29603	-1223.967691	-1223.671661
bpyCu_MeCN_2	-958.2030812	-957.932519	-958.006176	0.196905	-958.436719	-958.239814
Cu_OnPr_AZADO	-1367.554538	-1367.047856	-1367.131387	0.423151	-1367.876702	-1367.453551
Cu_OnPr_AZADO-ts	-1367.553284	-1367.049964	-1367.132477	0.420807	-1367.874266	-1367.453459

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